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THE IMPACT OF EPITHELIAL TO MESENCHYMAL TRANSITION IN KIDNEY FIBROSIS

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Abstract: *Fibrosis is a pathological condition attributed to an inappropriate deposition of extracellular matrix that promotes scarring and dysfunction of the implicated organ or tissue. Moreover, fibrosis encompasses an enormous range of organs and tissues, each with a distinct molecular basis. Yet, two factors are discussed: the critical function of transforming growth factor-beta (TGF-β) and the participation of the inflammatory cascade, which is required to initiate fibrotic destruction. Epithelial to mesenchymal transition (EMT), the most prevalent cellular program underlying fibrosis, is regulated by TGF-β, as well as other cytokines. EMT has been widely investigated, although it has not yet been adequately examined as a potential treatment option for fibrosis. A better knowledge of the linkages between fibrosis and EMT may provide an option for the establishment of a highly useful anti-fibrotic treatment. Thus, we provide a general overview of EMT; summarize the significance of TGF-β/Smad signaling cascade in EMT induction, the correlation between both EMT and renal fibrosis and the promising treatment strategies targeting fibrosis induced by EMT.*

Keywords: *Epithelial to mesenchymal transition, TGF-β/Smad, Snail, Kidney fibrosis.*

INTRODUCTION

Epithelial to mesenchymal transition

Epithelial to mesenchymal transition (EMT) is a widely recognized molecular mechanism that enables epithelial cells to undergo multiple biochemical changes in order to develop a mesenchymal phenotype. The ability of EMT to break down the basement membrane and produce mesenchymal cells that migrate from their initial epithelial layer is evidence of its progress[1]. This event is identified by a strong decline in the expression of particular epithelial proteins, like E-cadherin (E-cad) and zonula occludens-1, coupled with a considerable elevation in the production of different mesenchymal biomarkers, notably alpha smooth muscle actin (α-SMA), vimentin, and laminin[2].

Discovery and terminology of epithelial to mesenchymal transition

The concept of epithelial cells capacity to shift among epithelial and mesenchymal phases via EMT and mesenchymal to epithelial transition was first introduced by Elizabeth Hay in 1968[1]. Her research on the chick primitive streak model led her to the conclusion that epithelial cells undergo significant phenotypic alterations that reveal their "conversion" into mesenchymal cells. It was agreed to develop the term "EMT" at the inaugural conference of the International Association of EMT in Port Douglas, Australia, in 2003. This term is preferential over epithelial mesenchymal transformations, which were previously utilized, because it facilitates difference from neoplastic transformation and somewhat reflects process conversion (EMT-mesenchymal to epithelial transition)[1&3].

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Main features of epithelial and mesenchymal cells

Epithelial cells are polarised cells that commonly have polygonal morphologies. Their basal surfaces are connected to basement membranes that separate them from the connective tissues below, and their apical sides confront the lumen of a tubular structure or body cavity. On their lateral surfaces, joined to nearby epithelial cells by strong connections[4–6].

In general, mesenchymal cells are solitary, lack intercellular connections, exhibit a spindle-like appearance without indication of apicobasal polarity, and have the potential to migrate. They can express a variety of mesenchymal biomarkers, such as vimentin, fibronectin, and α-SMA[4&6].

Epithelial to mesenchymal transition types

Throughout early embryogenesis, EMT is a broadly recognized phenomenon that is thought to be crucial for mesoderm production. Additionally, EMT is detected in pathophysiological conditions, notably in healing process, tissue regeneration, organ fibrosis, and malignant transformation. Even though the recognized kinds of EMTs have a number of similarities, it is important to distinguish between EMTs that happen in various settings. Three distinct categories for EMT have been designed.

Type I EMT is utilized throughout developmental process to transform epithelial cells into cells exhibiting mesenchymal properties. It can be considered a "clean" and completely normal condition that does not accompanied by inflammation, fibrosis, or an invading characteristic. Conversely, type II EMT happens when tissue regenerates itself after suffering from a trauma or inflamed lesion. Under usual conditions, type II EMT is often restricted to an initial regeneration phase (such as wound healing) and might be advantageous since it promotes tissue renewal. Conversely, if proinflammatory stimulation continues, prolonged type II is accompanied by fibrotic action, that might result in organ damage. Lastly, EMT type III, which is related to cancers and in which EMT is the mechanism that promotes cancer invasion and progression capabilities. Type III EMT is characterized by the fact that it arises from cells which have previously experienced malignancy progression. Accordingly, tumor cells-specific genetic and epigenetic alterations, like oncogene induction and tumor suppressor deactivation, may be coordinated with the EMT mechanism[1].

Epithelial to mesenchymal transition markers

When epithelial cells develop EMT, they exhibit a considerable decline in the expression of epithelial biomarkers such as E-cad, some cytokeratins, occludin, and claudin as well as a substantial elevation in the expression of mesenchymal biomarkers notably α-SMA, N-cadherin, vimentin, and fibronectin[7].

Cell to cell connections and epithelial tissue morphology are preserved by E-cad. E-cad expression is diminished in all three kinds of EMT and is regarded as being the prototype hallmark of EMT. E-cad depletion promotes EMT via regulating cell to cell attachment as well as changing signaling via the sequestration of related cytoplasmic proteins such as β-catenin. Cadherin shifting, identified as a shift in the expression of various cadherins, has evolved like an indicator for EMT. Principally, EMT is frequently linked to a transition from E-cad to N-cadherin that is prevalent in mesenchymal cells, tumor cells, and neural tissue. Furthermore, a further point of concern for type II EMT related to fibrotic process is the shift from E-cad to OB-cadherin that is prevalent in myofibroblasts. Despite the fact that the processes driving cadherin shifting in the developmental and pathological conditions are yet unknown, the varied pattern of shifting between cadherins implies that external factors cause a change toward a more active adhesion status by inducing the formation of novel cadherins[8].

α-SMA, a mesenchymal marker, serves as one of the cytoskeletal proteins implicated in EMT type II. Growth factors govern the expression of this important biomarker, and it is expressed in fibroblast stress fibers, enhancing their contractile capacity, which is crucial for tissue remodeling[9&10].

Vimentin, like other cytoskeletal elements including microfilaments and microtubules, is a crucial type III intermediate filament protein. It is widely recognized that it serves a critical impact in several essential cellular activities like structural strength, adherence, motility, and signaling[11]. Vimentin is significantly expressed by harmed tubular epithelial cells, according to previous investigations, although this is thought to be a sign of regenerative capacity rather than EMT[12&13]. Wang et al. examined the significance of vimentin expression during the development of EMT-related kidney fibrosis through unilateral ureteral obstruction (UUO) in vimentin knockout animals as well as evaluated the quantity of fibrosis with the control animals. A same effect was observed in cultured human proximal renal tubular cells when vimentin expression was reduced through lentivirus-mediated suppression of vimentin and then treated with TGF-β that triggers the EMT program. Researchers indicated that suppressing vimentin prevents the fibrotic activity after UUO, presumably through downstream signaling cascades[14].

A glycoprotein with a large molecular mass called fibronectin contributes as a framework for fibrillar extracellular matrix (ECM). It has been considered to be a sign of type I EMT related to gastrulation, palate fusion, and neurulation since it is among the early elements to arise once the fibrillar ECM is produced. Despite being a crucial component of the desmoplastic stroma in cancers and the fibrotic ECM linked to tissue fibrosis, fibronectin's value as a type II and type III EMT indicator is constrained partly due to the fact that it is generated by a wide range of cell kinds, notably fibroblasts, mononucleated cells, and epithelial cells[4].

Transforming growth factor-β signaling pathway and epithelial to mesenchymal transition

EMT is a very sophisticated, dynamic, and gradual mechanism that alters cell architecture and requires appropriate molecular reprogramming in conjunction with additional biochemical regulations. As a consequence, the control of EMT is influenced by a variety of parameters. Several mechanisms that affect particular gene stimulation and repression, transduction signaling pathways, multiple important mediators are collaborating together to regulate EMT[15].

Considerable cross-talking is developed across different pathways that participate in multiple biochemical circuits. The most significant molecular change associated with EMT is the down-regulation of the expression of the epithelial biomarker E-cad, which is thought to be the "central regulator" of the EMT phenotype shift because it is the most crucial step in reducing cell-cell adhesion, which leads to disruption of epithelial cells' architecture[9].

One of the most documented pathways that implicated in the promotion of EMT is TGF-β signaling, which works through a variety of internal messengers. The TGF-β superfamily of ligands that incorporates the three TGF isoforms (TGF-β 1, 2, and 3), often stimulate signaling. TGF-β1 modulates EMT, particularly arises in fibrosis and tumor[16]. Endothelial to mesenchymal transition is predominantly coordinated by TGF-β 2 throughout cardiac development[17] and TGF-β 3 governs EMT in the developing palate[18].

The TGF-β1/Smad/Snail pathway, which is induced throughout TGF-triggered EMT and ends in the EMT-dependent fibrotic activity in a variety of illnesses, represents an extremely noteworthy pathway[19&20]. All three forms of TGF-β utilize the similar receptors: type I (RI, or Activin receptor-like kinase 5), type II (RII), and type III (RIII, or betaglycan). TGF-β1 signaling cascade is started when TGF-β1 binds to RIII, then recruits to RII which facilitates the trans-phosphorylation process and excitation of RI. The Smad signaling allows the phosphorylation of receptor-regulated Smads (R-Smads or Smad2/3), which subsequently form a heterogenic combination alongside Smad4 and concentrates inside the nucleus to govern the target genes expression thought to be participate in the progression of EMT via the stimulation of transcription factors[21] as shown in **Figure 1**.

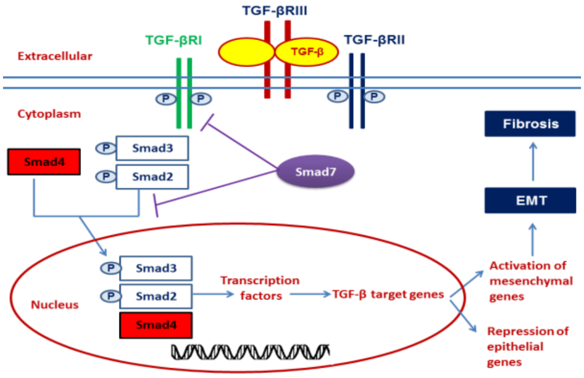

Fig. 1: TGF-β/Smad signaling pathway.

For instance, the genes that code for the zinc finger transcription factor Snail, were efficiently stimulated for transcription[22]. Snail acts a crucial function in directing the EMT phenomenon that incorporates the depletion of epithelial biomarkers, like E-cad and claudins as well as concurrent overexpression of mesenchymal biomarkers, like vimentin and fibronectin[23&24]. In a study utilizing Madin-Darby canine renal cells that had been exposed to TGF-β1, Peinado et al. convincingly showed that Snail seems to be a potent suppressor of the expression of the epithelial biomarker E-cad. The fact that such cells initiated an EMT process that has been induced by TGF-β1 implies that Snail is a particular goal of TGF-β1signaling[25].

Inhibitory Smads (I-Smads) are elements of the Smad family that suppress intracellular TGF-β signaling via interacting with activated type I receptors and receptor-regulated Smads (R-Smads). Smad7 is categorized as I-Smad since it acts as a negative regulator of the TGF-β-evoked EMT. I-Smads can disrupt interactions among R-Smads and type I receptors, induce downregulation of cell type I receptor expression, hinder complex formation by R-Smads and Smad4 (**Figure 1**), and govern Smads-dependent transcriptional regulation inside the nucleus[26]. Smad7 prevents TGF-β-evoked EMT in different tissues[27&28].

Epithelial to mesenchymal transition and its role in kidney fibrosis

Although it is well recognized that myofibroblasts are the principal cells involved in the process of extensive interstitial ECM buildup that emerges under pathological states, there is still much debate over their source[29&30]. In-depth research has been done on the pathways concerned in activating the myofibroblasts that generate matrix in the fibrotic kidney. The initial evidence for a link between fibrosis and EMT emerges from the finding that epithelial cells able to generate many fibroblast specific biomarkers as well as experience morphological variations in disease conditions which are distinctive to fibroblasts[29]. The inappropriate development of the fibroblast-specific protein in the epithelial cells of renal tubules driven Strutz et al. to speculate that these myofibroblasts may be generated by altered epithelial cells[31]. The curiosity about the process of EMT in kidney reinforcing additional with the affirmation of such a principle because Iwano et al. indicated that close to 36% among all myofibroblasts in a UUO model was evolved during kidney fibrosis from tubular epithelial cells via EMT[32].

TGF-β1 promotes tubular and glomerular EMT and excessive ECM synthesis and deposition in the glomeruli and tubulointerstitium[33]. TGF-β1 is substantially expressed in a variety of renal disorders linked with fibrosis[34]. The activities of TGF-β1 on renal fibrosis and EMT were further reinforced by the findings that overexpression of active TGF-β1 in the liver produces severe kidney fibrosis in mice[35]. Conversely, anti-TGF-β treatment options utilizing neutralizing antibodies[36], inhibitors against TGF-βRII[37], or antisense oligonucleotides to TGF-β1[38] block the progression of kidney fibrosis, indicating a crucial pathological impact of TGF-β in chronic kidney disease.

The therapeutic impact of EMT was also revealed in a research characterizing renal biopsies: a substantial association was identified among epithelial cells with EMT characteristics, the amount of interstitial fibrosis, and renal functional loss[39]. Additionally, Snail expression has been identified in locations with substantial collagen deposition in nephrectomy samples from individuals with urinary obstruction[40]. Furthermore, epithelial-derived myofibroblasts have been linked to a variety of kidney illnesses, including diabetic kidney disease, glomerulonephritis, spontaneous lupus nephritis, chronic allograft nephropathy, and glomerulonephritis[41]. Thus, preventing the kidney from initiating EMT is considered a crucial barrier against further fibrosis.

Looking for drugs or natural agents to establish new anti-EMT therapies is currently an interesting concept. For example, an antifibrotic impact for the regularly prescribed anti-tumor medication paclitaxel has been reported, by suppressing Smad2/3, JNK and ERK1/2 stimulation and diminishing renal fibrosis in TGF-β1-induced murine cells[42]. By a notable reduction in TGF-β1, collagen I, and α-SMA levels, the antianginal drug nicorandil has been demonstrated to improve kidney fibrosis progression[43]. Azilsartan, an antihypertensive drug, attenuated cisplatin-evoked EMT via influencing of TGF-β1/Smad /Snail signaling cascade[44].

Resveratrol, a natural compound, can protect the kidney from gentamicin-evoked EMT through modulating TGF-β/Smad signaling cascade[45]. Additional research has indicated that baicalin, a flavonoid derived from Scutellaria baicalensis, exhibits a therapeutic impact against renal fibrosis. Baicalin blocks EMT by diminishing TGF-β1 and the subsequent signal pathway, involving Smad2/3, as indicated by modifications in kidney shape and the expression of essential EMT proteins[46]. Another natural agent that has anti-fibrotic properties is Ribes Diacanthum Pall. In a kidney fibrosis model, it has been noticed that it diminishes EMT via attenuating levels of p-Smad2/3, α-SMA, collagen I and fibronectin[47]. Furthermore, Cili freeze-dried powder successfully diminishes kidney fibrosis which is linked with the attenuation of TGF-β1/Smad pathway[48]. Lastly, asperulosidic acid, an iridoid glycoside derived from Hedyotis diffusa, showed a variety of positive properties in a UUO model, as well as guards against kidney fibrosis via lowering inflammatory protein levels and modulating TGF-β1 signaling[49].

Conclusion

Unrestricted fibrosis is a sophisticated condition which may be triggered by a variety of pathways with considerably diverse molecular bases in various organs and tissues. This is a significant barrier to the establishment of generally useful anti-fibrotic agents. Nevertheless, we have summarized in this review, the evidence of the participation of TGF-β /Smad signaling cascade implicated in EMT promotion and kidney fibrosis. Hence, we postulate that interrupting of TGF-β /Smad signaling cascade governing EMT might open up new approaches for the establishment of highly efficient anti-fibrotic treatments.

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تأثير التحول الطلائي الوسيط في تليف الكلى

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التليف هو حالة مرضية قد يؤدي إلى خلل وظيفي للأعضاء أو الأنسجة المصابة. علاوة على ذلك، يشمل التليف مجموعة هائلة من الأعضاء والأنسجة، لكل منها مسار جزيئي خاص. عامل النمو المحول بيتا (TGF-β) يعتبر واحد من أهم عوامل الحث علي التحول الطلائي الوسيط. التحول الطلائي الوسيط هو البرنامج الخلوي الأكثر انتشارًا الكامن وراء التليف، وهو يدفع الخلايا الطلائية إلى التحول إلى خلايا وسيطة. و يتطلب تحويل الخلية الطلائية إلى خلية وسيطة تغيرات في الشكل بالإضافة إلى زيادة التعبير عن العلامات الجزيئية الخاصة بالخلية الوسيطة ونقص العلامات الجزيئية الخاصة بالخلية الطلائية. التحول الطلائي الوسيط الذى يحدث بعد إصابة كلوية يُفترض أنه مصدر للخلايا الليفية العضلية التي تحتل النسيج الخلالي الكلوي وتعزز التليف. قد توفر معرفة أفضل للعلاقة بين التليف و التحول الطلائي الوسيط خيارًا لإنشاء علاج مضاد للتليف. وبالتالي، فإننا نقدم لمحة عامة عن التحول الطلائي الوسيط؛ تلخيص أهمية سلسلة إشارات مسار عامل النمو المحول (بيتا/ سماد TGF-β/Smad) في تحفيز التحول الطلائي الوسيط، والعلاقة بين كل من التحول الطلائي الوسيط والتليف الكلوي واستراتيجيات العلاج الواعدة التي تستهدف التليف الناجم عن التحول الطلائي الوسيط.