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Research Progress of Each Cell Signaling Pathway in Renal Interstitial Fibrosis and Anti-Fibrotic Intervention Countermeasures

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Abstract: Interstitial fibrosis is a common pathological feature of various progressive renal diseases, andthis result is mainly caused with the activation of renal interstitial innate cells (fibroblasts, pericytes, immune cells, mesenchymal stem cells, etc.) and the massive expression and deposition of extracellular matrix（ECM）. According to statistics,chronic kidney disease and interstitial renal fibrosis affect half of the world's adults over the age of 70 and 10% of the population.Although there are currently no drugs or other means to halt this process, as more and more key players affecting fibrosis are identified, this provides new research directions for anti-fibrotic therapy. In this review, we highlight the relationship between renal interstitial lamina propria and the progression of interstitial fibrosis and describe new advances in anti-fibrotic strategies.Finally,we hope to provide new ideas for the treatment of interstitial renal fibrosis.

Keywords: Interstitial Kidney; Fibrosis; Fibroblasts; Pericytes; Anti-Fibrosis; Mirna

1. Introduction

The renal interstitium is the space between the renal tubules,outside the glomerulus, and outside the renal vasculature[1]. It is surrounded on all sides by tubular and vascular basement membranes, which are filled with mesenchymal cells (dendritic cells (DC), lymphocytes and various types of fibroblasts), extracellular matrix (ECM) and interstitial fluid[2-4]. Fibrosis is a pathological extension of the normal wound healing process, and it can be dissolved and absorbed during minor injuries. However, in the process of chronic injury, fibrous degradation in the organ is weaker than expression generation, and activation of fibroblasts leads to massive expression and deposition of ECM. This leads to the destruction of organ structure and impaired organ function[5]. Fibrosis can occur not only in the kidneys but also in the heart, lungs, liver, digestive tract and other organs.It has been shown that non-mesenchymal cells (epithelial cells, macrophages/monocytes, endothelial cells) express only a small amount of ECM genes, andmost ECM is derived from mesenchymal cells[6].Mesenchymal cells play a decisive role in renal interstitial fibrosis.Here, we describe the connection between mesenchymal cells and renal interstitial fibrosis, and summarize the treatment of renal interstitial fibrosis. We hope to provide new ideas for all scholars to study anti-interstitial renal fibrosis.

2. Fibroblasts andrenal fibrosis

Kidney fibroblasts (KF) are the main site of ECM production in renal interstitial fibrosis[7].It receives TGF-β1 stimulation and eventually transforms into myofibroblasts through the classical TGF-β/Smad pathway, or non-classical

TGF-β/Smad pathways such as MAPK, ERK/JAK signaling pathways[8-11].A new study found that the endoplasmic reticulum protein TXNDC5 is required in the TGF-β1-induced activation of human kidney fibroblasts (HKF), and its overexpression is sufficient to promote HKF activation, proliferation, and collagen production, ultimately promoting fibrosis. And it was demonstrated that deletion of TXNDC5 slowed the progression of renal fibrosis, suggesting the potential of TXNDC5 for the treatment of interstitial fibrosis and chronic kidney disease(CKD)[12].In addition, Wang et al.[13]demonstrated that pharmacological inhibitors or siRNA targeting DRP1 could inhibit the expression of α-SMA and type I collagen.In a study of non-melanoma skin cancer, activator A was found to promote the binding of Smad2/3 to the "Smad-binding element" in the first intron of the mDia2 gene, which activates fibroblasts and eventually differentiates into different tumor-associated fibroblast subtypes[14]. Although the pathway of activation is different from that of normal fibroblasts, it can be a new direction for anti-fibrotic research.

In 2017, Mark et al.[15] proposed a third path of renal interstitial fibrosis:aberrant endothelial secretory proteins such as pro-fibrotic signals (Notch and ligands of the Wnt/β-catenin pathway). Studies have confirmed that tubule-derived WNTs are required for KF activation and interstitial fibrosis, and that Wnt plays a major role in driving MYO activation and renal fibrosis[16, 17].Experimental studies have confirmed that β-catenin in fibroblasts is increased by WNT protein stimulation and acts as a transcriptional co-activator together with TCF/LEF[18].β-catenin promotes the activation of fibroblasts and enables the migration and proliferation of MYO[19, 20], which ultimately leads to interstitial fibrosis.

3. Pericytes andrenalfibrosis

In the kidney, perinephric cells are divided into renin-producing perivascular cellsand perivascular cells, the former is capable of synthesizing, storing and secreting renin, and it activates the renin-angiotensin-aldosterone system (RAAS) and regulates renal medullary and cortical blood flow;the latter is a precursor cell of MYO and plays an important role in the remodeling of microvessels and the development of interstitial fibrosis [1, 6, 21-23].In CKD, chronic activation of the RAAS system leads to renal oxidative stress and inflammatory responses, ultimately promoting interstitial fibrosis[24-26].With the activation of the RAAS system, angiotensin-converting enzyme 2 (ACE2) exhibits a protective effect on the kidney by converting angiotensin 2 (Ang2) to Ang1-7, reducing inflammation and fibrosis[27].Furthermore, CHOU et al. [28]showed that hypermethylation of pericytes promoted the progression of acute kidney injury (AKI) to CKD, and 5-azacytidine demethylation reversed the pro-fibrotic properties of pericytes.

4. Immune cells and renal fibrosis

Inflammatory immune responses also contribute to fibrosis.In the development of interstitial renal fibrosis, various types of immune cells are recruited into the kidney, including macrophages, T cells, DCs, and mast cells[29].B cells are also important players in this, influencing fibrosis through the production of cytokines (IL-36, IL-17, IL-23, etc.) and interactions with other immune cells[3, 30].In astudy of IgA nephropathy, TLR7 was highly expressed in$CD19^+$B cells and was strongly expressed in the tubulointerstitial and periglomerular regions[31], which may correlate with the extent of renal interstitial fibrosis.FMS-like tyrosine kinase 3 ligand (FLT3L) stimulates the development of DCs, and FLT3L-dependent DCs promote the activation and accumulation of renal effector T cells aggregation, which leads to renal oxidative stress and ultimately promotes interstitial fibrosis[32].In renal transplantation[33], macrophages are converted to MYO via the TGF-β1/smad3 signaling pathway, and we can intervene in TGF-β1 downstream pro-fibrotic signaling molecules (JAK3, STAT6, etc.) for anti-fibrotic treatment[34].

5. Mesenchymal Stem Cells (MSCs) andrenalfibrosis

MSCs are present in the perivascular areas of many organs, including the kidney, lung, liver and heart. A study showed that Gli1 was able to label MSCs, and after kidney injury, $Gli1^+$ cellsproliferated, differentiated into MYO, and promoted renal interstitial fibrosis[35].However, several studies have shown the role of MSCs in reducing liver fibrosis, lung fibrosis, and corneal fibrosis have been demonstrated[36-39], and it has a preventive effect on renal fibrosis in mice with ischemia-reperfusion [40].This allows us to suggest that stem cell therapy may be a new therapeutic route for interstitial

fibrosis in the kidney.

6. Cellular aspects of therapeutic interventions for progression of interstitial renal fibrosis

6.1 Fibroblast aspects

Currently, the anti-interstitial renal fibrosis drugs mainly target known key players in the molecular mechanisms (mainly targeting fibroblast signaling pathways), such as transforming growth factor (TGF)-β, connective tissue growth factor (CTGF), bone morphogenetic protein (BMP)-7, endothelin-1, SMAD3 and 4, and NADPH oxidase (NOX) 1 and 4[41].Ruxolitinib[42], a potent and selective inhibitor of JAK1 and JAK2, was applied to unilateral ureteral obstruction (UUO) mice and TGF-β1-treated cells. It inhibits activation of mouse renal fibroblasts, ECM production and TGF-β1-treated fibroblasts, attenuates the activation of STAT3 and Akt/mTOR/YAP pathways.Discoidal structural domain receptor 1 (DDR1) is a receptor tyrosine kinase activated by collagen. The Borza experiment demonstrated that DDR1 is upregulated during renal injury, whichphosphorylating STAT3 and activating the TGF-β/Smad pathway, this leads us to speculate that DDR1 could be a new anti-fibrotic target[43].In the course of research on herbal medicines, Salidroside[44] and Rhein[45] have also been shown to slow the progression of interstitial fibrosis by partially blocking the phosphorylation of STAT3.

6.2 Pericellular aspects

PDGFR-β^+ pericytes are the main source of scar-forming myofibroblasts[46].Studies have confirmed that STAT3 is a key transcription factor involved in renal interstitial fibrosis, which not onlypromotes fibrosis by increasing inflammation, fibroblast and macrophage activation, but also by modulates pro-fibrotic signaling in pericytes.By studying STAT3 knockout or inhibited mouse, Ajay et al.[47] found that STAT3 deletion inhibited the transformation and migration of perinephric cells and saved mouse from interstitial kidney fibrosis injury, this provides evidence for STAT3 as a new target for therapy.Notably in RAAS, dual RAAS blockade is more effective than single RAAS blockade with minimal side effects[48].Jin et al. found that by injecting hepatic stellate cells (HSCs) and renal stellate cells (RSCs) with albumin and its derivative retinol-binding protein-albumin structural domain III fusion protein (R-III) could interfere with the process of interstitial fibrosis in the mouse kidney [49].Additional studies have demonstrated that low levels of vitamin D receptors and their activators could lead to secondary hyperparathyroidism and worsening of interstitial fibrosis. Paricalcitol (an antiparathyroid drug)[50] is effective in reducing interstitial fibrosis through inhibition of RAAS, inflammation and epithelial-mesenchymal transition.These studies illustrate that blocking the conversion of pericytes to MYO and inhibiting RAAS system activation would be promising therapeutic approaches to prevent interstitial renal fibrosis.

6.3 Other modes of intervention

6.3.1 Antioxidant therapy

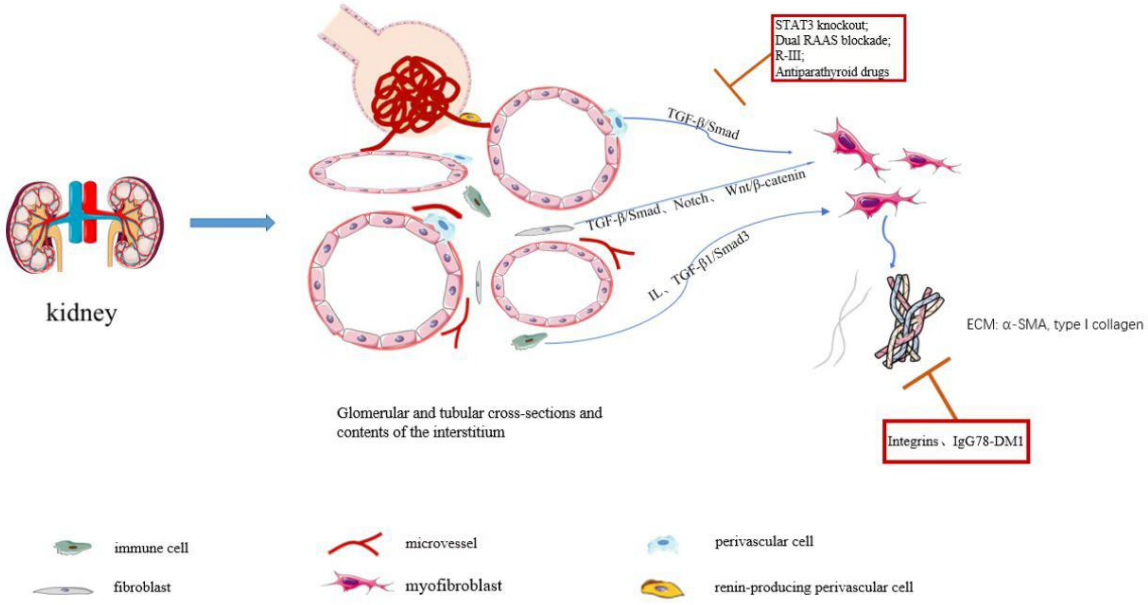
In interstitial renal fibrosis, oxidative stress is also an important causative factor.N-acetylcysteine (NAC)[51], Pterostilbene (Pts, a bioactive component in blueberries)[52] both have anti-inflammatory and antioxidant effects, the former attenuates renal interstitial fibrosis through Sirtuin1 (SIRT1) activation and p53 deacetylation, and the latter interferes with the progression of pulmonary fibrosis by affecting lipopolysaccharide (LPS).SIRT1 activation and p53 deacetylation can be potential targets to attenuate premature renal failure after AKI and delay CKD progression[51].5-methoxytryptophan (5-MTP) is an innate anti-inflammatory metabolite and an endogenous molecule metabolized by tryptophan via the tryptophan hydroxylase pathway.Recent studies have confirmed that 5-MTPis effective in attenuating injury-induced liver, kidney, heart and lung fibrosis, itcould inhibit macrophage activation and prevent fibroblast form differentiating into MYO[53].

6.3.2 Gene therapy (miRNA intervention)

In the experimental study of renal interstitial fibrosis, two miRNAs (miR-27b-3p and miR-1228-3p)[54] were found to be candidate biomarkers of renal interstitial fibrosis.We can target and regulate TGF-β, SMAD, WNT10a and other pathways or proteins by up- or down-regulating miRNAs to achieve anti-fibrotic results[55].In MSCs[37], miRNAs attenuate fibrosis and inflammation through extracellular vesicle-mediated delivery; in T cells[56], miRNA-214 induces the production of pro-fibrotic cytokines (IL-17, TNF-α, IL-9, and INF-γ) and chemokine receptors (CCR1, CCR2, CCR4, CCR5, CCR6, and CXCR3) to influence fibrosis progression.Besides the kidney, miRNA also plays an important role in the treatment of liver fibrosis[55] and cardiac fibrosis[57]. All of these show that RNA interventions have great advantages in the treatment of fibrosis.

6.3.3 Protein and peptide therapy

Integrins are cell surface protein receptors consisting of α and β subunits, they participate in a variety of cellular functions, such as adhesion and anchoring to the ECM, TGF[58].Among them, αv integrins have proven to affect fibrosis by regulating TGF-β1 activity.Several studies confirms that integrin antibodies are protective against CCl-4-induced hepatic fibrosis,unilateral ureteral obstruction (UUO)-induced renal fibrosis and bleomycin-induced pulmonary fibrosis [59].CD248 is a type I transmembrane glycoprotein and it ishighly expressed and specific expression in MYO of CKD patients[60, 61].Xu et al.[62] found that an antibody-drug conjugate called IgG78-DM1, which specifically killed CD248^{+}MYO and had a good anti-fibrotic effect in mice with renal interstitial fibrosis. From this, we can guess that antibody-drug combinations may have better efficacy than single antibodies, which provides a new idea for anti-fibrosis.In the trend of new coronary pneumonia pandemic, SARS-CoV-2 virus was found to directly infect kidney cells and cause interstitial fibrosis, the protein and peptide therapy provides feasibility for anti-COVID-19 interstitial fibrosis[63].



7. Summary

In summary, we can find that the renal interstitium is the interstitial space between the renal tubules, outside the glomeruli, and outside the renal blood vessels.With the increasing maturity of cellular studies, it is found that the main

influences on interstitial fibrosis are fibroblasts and pericytes.On the one hand, renal interstitial fibrosis is caused by renal interstitial innate cells through TGF-β/Smad signaling pathway and RAAS system activation, leading to MYO proliferation and a large amount of ECM being expressed; on the other hand, pro-fibrotic cytokines (IL-17, TNF-α, IL-9 and INF-γ) and chemokine receptors (CCR1, 2, 3, 4, 5, 6 and CXCR3) affect the inflammatory response and oxidative stress in the kidney, promoting the process of interstitial fibrosis.Although there are no clinically effective drugs for the treatment of interstitial renal fibrosis, new advances in targeted cellular, anti-inflammatory antioxidant, and genetic anti-fibrotic therapies continue to be made.

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