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Research Progress of Traditional Chinese Medicine in Treating IgA Nephropathy through Notch Signaling Pathway

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Abstract: IgA nephropathy is one of the most common primary glomerular diseases, with a high incidence and varying clinical manifestations. The Notch pathway is an important cell signaling pathway that regulates cell differentiation, proliferation, development and apoptosis, and plays a key role in many developmental processes, including kidney development. A number of experimental studies have confirmed that the Notch signaling pathway is closely related to IgA nephropathy and is an important pathway involved in the pathogenesis of IgA nephropathy. In recent years, with the study of the active ingredients of traditional Chinese medicine(TCM), a large number of experimental and clinical studies have confirmed that TCM has unique advantages and curative effects in preventing and treating IgA nephropathy. Since there are relatively few studies on the use of TCM in the treatment of IgA nephropathy related to the Notch pathway, this article mainly introduces the related mechanism research of Notch signaling pathway involved in IgA nephropathy, and summarizes the relevant research on the regulation of Notch signaling pathway and anti-fibrosis of Chinese medicine ingredients in IgA nephropathy.

1. Introduction

As the most common primary glomerular disease, IgA nephropathy has a high incidence in Asia, and it is increasing year by year. About 20% of patients progress to end-stage renal disease 10 years after onset [1]. The disease is often found in physical examination, with insidious onset and variable clinical manifestations. It is characterized by recurrent gross hematuria or microscopic hematuria, or accompanied by varying degrees of proteinuria, hypertension, and renal impairment [2]. IgA nephropathy is an immune-mediated chronic inflammatory disease based on the deposition of IgA-based immune complexes in glomeruli [3]. With the deepening of research on the pathogenesis of IgA nephropathy, it has been found that IgA nephropathy may be closely related to genetic inheritance, immune inflammatory stimulation, and cytokine effects [4,5]. At present, the overall goal of IgA nephropathy treatment is to reduce proteinuria, control blood pressure, slow down the progress of

kidney disease, and delay the occurrence of ESRD. Clinical studies have also confirmed that t TCM has unique advantages and curative effects in preventing and treating IgA nephropathy.

2. Notch signaling pathway

Notch signaling pathway consists of Notch receptors, DSL proteins, CSL, related regulators, and intracellular effector molecules together constitute a complete signal transduction pathway, including 4 source receptors Notch1~4, 5 DSL proteins (DLL1, DLL3 , DLL4, Jagged1, Jagged2), receptors and ligands are all single transmembrane proteins. It is worth noting that its ligands are membrane proteins. The Notch pathway communicates with adjacent cells, and then participates in the regulation of cell development, proliferation, regeneration/repair, differentiation, apoptosis and other processes. After the Notch ligand binds to the receptor, it is cleaved sequentially by the ADAM metalloprotease at site S2 and the γ-secretase complex at site S3. In the intracellular domain of Notch, Nicd is released and enters the nucleus, where it interacts with CSL Combined to form Nicd-CSL complex, thereby regulating the transcription of target genes (such as Hes, Hey). Without Nicd, CSL is inhibited from degrading. Regulation of the Notch pathway is complex and occurs at many different levels. The most important is ligand binding, followed by γ-secretase-mediated cleavage [6,7].

3. Notch signaling pathway and kidney

Notch pathway is an important cell signaling pathway, which regulates cell differentiation, proliferation, development and apoptosis. Plays a key role in many developmental processes, including the development of the kidney. Notch signaling plays multiple roles in the development of the mammalian kidney. In recent years, studies have shown that the Notch signaling pathway is involved in the entire process of kidney development and is expressed in all stages of the pronephros, mesonephros and metanephros [8]. Studies have found that Notch1 and Notch2 receptors are expressed in renal tubules and glomeruli, and the ligands Delta1 and Jagged1 are expressed in the early development of renal tubules [7]. The lack or reduction of Notch signaling in the body will lead to abnormal development of the kidney. Once the kidney tissue matures, the notch signaling pathway will be inactivated, so the expression of Notch signaling in the adult kidney is significantly reduced. In addition to participating in the development of the kidney, the Notch signaling pathway also plays a role in coordinating tissue damage and repair [9]. Studies have found that abnormal activation of Notch3 can promote epithelial cell proliferation, leading to cyst formation and growth, and Notch-3 is involved in tubulointerstitial injury and inflammatory response [10-11]. Related studies have demonstrated the activation of the Notch pathway in tubulointerstitial fibrosis (TIF) patients and TIF mouse models. The increase in Notch1 and Jag1 mRNA levels in previous studies has further demonstrated the increased expression of the kidney-specific target gene HeyL, showing for the first time that, increased Notch signaling in renal TECs plays a functional role in TIF development [12]. Niranjian [13] showed that Notch1 signaling is activated in podocytes of human patients affected by diabetic nephropathy (DN) and focal segmental glomerulosclerosis (FSGS). Therefore, it shows that Notch signaling has a complex regulatory mechanism for the kidney, and has a bidirectional regulatory function in the process of tissue repair and regeneration. Studies have confirmed that the Notch signaling pathway plays a role in acute renal failure, renal interstitial fibrosis, diabetic nephropathy, focal segmental sclerosis glomerulonephritis and other renal diseases through inflammation, apoptosis, epithelial-mesenchymal cell transdifferentiation and other mechanisms Play an important role [14].

4. Renal fibrosis

Renal fibrosis is a common pathological process of various renal diseases progressing to the end stage, characterized by glomerulosclerosis and tubulointerstitial fibrosis, mainly the accumulation of myofibroblasts and ECM components. The excessive production and deposition of β, leading to the progressive loss of renal function [15]. The occurrence of renal fibrosis involves many links such as inflammatory response, apoptosis of renal intrinsic cells and immune cells, oxidative stress response, and imbalance of cytokines that promote/inhibit fibrosis [16]. Under the stimulation of complement and immune complexes, pro-inflammatory factors are released, which leads to the infiltration of a series of inflammatory cells into the mesangial area, vascular area, and renal interstitial area, triggering an inflammatory response, which in turn promotes the phenotype of renal intrinsic cells. Transformation, the release of nephrotoxic factors and growth factors promotes the occurrence of renal fibrosis [17]. Inflammation can trigger oxidative stress in the body, resulting in apoptosis and activation of inflammatory cells. Sustained damage will cause infiltration of macrophages and immune cells. In this chronic inflammatory environment, cytokines and growth factors are released in large quantities, including Transforming growth factor-β (TGF-β) family members and Wingless/Int-1 (Wnt1), TGF-β and Wnt1 bind to their stem cell surface receptors and induce activation of downstream signaling Smad2/3, which in turn mediates upregulation of target gene expression, to further enhance myofibroblast differentiation and the production and secretion of ECM proteins [18].

5. Notch signaling pathway and IgA nephropathy

Notch signaling pathway may cause the occurrence and development of IgA nephropathy by participating in the regulation of renal cell differentiation, inflammatory response and fibrosis progression. It is mainly manifested in the apoptosis of podocytes, epithelial-mesenchymal transition (EMT) of renal tubular cells, proliferation of renal fibroblasts and production of extracellular matrix proteins [19]. Renal fibrosis is a risk factor for the progression of IgA nephropathy to end-stage renal disease, and is closely related to renal prognosis. IgA deposited in glomeruli is the basis of IgA nephropathy. It induces the activation of inflammatory factors, chemokines, and fibrosis factors, and activates Notch Signaling pathways interact with downstream pathways, ultimately causing renal fibrosis. Angiotensin-II (AngII), hypoxia-inducible factor-1 (HIF-1), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), endothelin (ET-1) , platelet-derived growth factor (PDGF), and connective tissue growth factor (CTGF) all play an important role in renal fibrosis [20].

Related studies have found that the expression of Notch1 and Jagged1 in the renal tissue and peripheral blood of patients with IgA nephropathy increases with the progression of the disease, increasing the expression of renal tubular atrophy and the development of renal interstitial fibrosis, which proves that the Notch signaling pathway can induce EMT and TIF It is involved in tubular atrophy and renal tissue fibrosis in IgA nephropathy [21]. In patients with IgA nephropathy, the expressions of Notchl, Jaggedl, and serum PDGF and Col-I are positively correlated with renal interstitial fibrosis. Process of fibrosis [22]. Tan [23] studied the effect of Notch signaling pathway on the number and function of peripheral blood Th17 cells in the process of renal interstitial fibrosis in rats with IgA nephropathy. The results showed that Notch signaling pathway and TGF. The -β signaling pathway was significantly abnormally activated. After the intervention of rat PBMCs with DAPT and TGF-β inhibitors, the expression levels of Notch1, TGF-β and related proteins were significantly reduced, and the Notch signaling pathway can also affect the number of Th17 cells and control its function. In patients with IgA nephropathy, Notch1, Jagged1, Hey1, and Hes1 were all expressed in renal tissue, and with the aggravation of renal interstitial fibrosis, the expression gradually increased, and the levels of Notch1 and Jagged1 in peripheral blood also increased. It shows

that Notch signaling is involved in the further occurrence and development of the disease, mainly through the activation of the Notch1/Jagged1 signal transduction pathway, causing the process of renal fibrosis [24].

6. TCM's understanding of IgA nephropathy and renal fibrosis

IgA nephropathy belongs to the category of edema, hematuria, kidney wind, lumbago, asthenia, etc. in traditional Chinese medicine. The location of the disease is in the kidney, which is closely related to the lung, spleen, liver, and triple burner, the standard is mainly damp-heat, blood stasis, and turbidity [25]. Insufficient righteousness, re-exposure to wind, dampness and other exogenous pathogens induce the primary disease, or the primary disease persists for a long time, or other diseases are untreated or mistreated, resulting in prolonged illness and blood stasis, prolonged illness enters the collaterals, stasis of the kidney collaterals, blood stasis Mutual accumulation of poisons, dereliction of qi transformation, failure of sealing and storage, leading to a series of dysfunctions such as the kidney governing the storage of essence, governing water, and governing qi transformation. Renal fibrosis is a modern medical concept. In recent years, Chinese medicine has expounded more on the mechanism of renal fibrosis based on the "theory of good and evil". It is believed that the pathogenesis of renal fibrosis is based on the deficiency of the spleen and kidney. As the pathological basis, positive and negative are intertwined with real and evil, forming a vicious circle over time. According to its pathological characteristics, clinical manifestations, etc., it can be classified into categories such as "edema", "closed grid", "disease", "intoxication", and "deficiency, stasis, dampness, poison" can be summarized as its main pathogenesis [26], similar to the symptoms of edema, oliguria and anuria, vomiting, fatigue, anorexia, dark complexion, and uremia that occur in the late stage of renal fibrosis in modern medicine.

Therefore, the prescription of clinical syndrome uses more tonifying and invigorating drugs [27], taking warming yang, activating blood circulation and dredging collaterals as the basic treatment principle, taking traditional Chinese medicine of tonifying kidney and spleen, warming kidney and strengthening yang, activating blood circulation and removing blood stasis, and cooperating with medicine-separated moxibustion at Dazhui, Mingmen, Shenshu, Pishu and other acupoints to penetrate evil and go out [26]. Combined with the physical characteristics of patients, a personalized treatment plan was adopted. By regulating the balance of yin and yang, improve the overall state of the body, improve the damage of the kidney. In addition, the combination of good living habits, diet and moderate exercise can also help to improve the kidney condition. With the in-depth study of anti-renal fibrosis at different levels and targets, such as compound prescription of traditional Chinese medicine, single traditional Chinese medicine and traditional Chinese medicine components, some progress has been made in the interpretation of related mechanisms. It provides the possibility for the sequential development of clinical and basic research, prescription optimization, screening of effective components and so on.

7. TCM regulation of Notch and renal fibrosis in IgA nephropathy

Long-term clinical practice has found that traditional Chinese medicine has certain advantages in the treatment of IgAN, and TCM has played a certain role in inhibiting the deposition of IgA, reducing the expression of inflammatory factors in renal tissue, and reducing mesangial hyperplasia [28,29]. In recent years, more and more studies have shown that TCM ingredients and compound prescriptions can improve the symptoms and development of the disease by regulating the Notch pathway [30,31], but there are relatively few studies on the treatment of IgA nephropathy therapeutic effect.

7.1. Total flavones of Abelmoschus manihot L.Medic

The flower of Abelmoschus manihot(L.)Medic was first recorded in "Jiayou Materia Medica", and recorded in "Compendium of Materia Medica": the smell of its flowers is sweet, cold, slippery, and non-toxic, and it is mainly used for "urinary strangulation and birth promotion. For those who treat various malignant sores and pus that do not heal for a long time, they will heal after the last application. Medicine. Relieves carbuncle. Soak in oil and apply soup to burn wounds". Modern research [32] has found that the main active ingredients of Abelmoschus manihot(L.)Medic are flavonoids, which can protect kidney podocytes, anti-inflammation, anti-fibrosis, anti-oxidation, reduce circulating immune complexes and other pharmacological effects, and achieve the purpose of reducing proteinuria and improving kidney function. Zhao [33] observed the related effects of total flavones of Abelmoschus manihot L.Medic on rats with IgA nephropathy, and found that the levels of urinary red blood cells, BUN, 24hUTP, and Scr in each dose group of total flavonoids decreased, and the levels of Notch1, Jagged1, TGF-β1, p -Smad3, Notch1mRNA, Jagged1mRNA expression decreased. The total flavonoids of ambrette can block the Notch signaling pathway, and inhibit the expression of Notch1, Jagged1, TGF-β1, and phosphorylated (p)-Smad3 proteins, thereby inhibiting glomerulus enlargement and reducing the precipitation of renal protein, thus the therapeutic effect on IgA nephropathy

7.2. Oridonin

Rabdosiar ubescens is a plant of the genus Fragrant Tea of the Lamiaceae. It is slightly cold in nature and has the effects of promoting blood circulation and relieving pain, relieving heat and noise, and clearing heat and detoxification. In recent years, research has found that oridonin is the main active ingredient of Rabdosiar ubescens, which has antihypertensive effects, such as antihypertensive, anti-oxidation, antibacterial, anti-tumor, anti-apoptosis, enhancing body immunity and so on [34]. Yan [35] administered oridonin (15mg/kg) in the AKI mouse model, and found that it could also improve the pathological damage of the kidneys of the mice, and reduce the inflammatory factors F4/80, IL-1β, iNOS and MCP- 1 expression. Xu [36] observed the related effects of oridonin on IgA nephropathy rats, and found that the 24h urinary protein, serum Scr, serum BUN and renal tissue The expressions of TNF-α, IL-6, IL-1β, MDA, Notch1 and Hes1 decreased, and the levels of SOD and GSH-Px increased, suggesting that oridonin may inhibit the Notch1 signaling pathway, thereby reducing the inflammatory response and oxidation in rats. Stress level, protect against renal tissue damage in IgA nephropathy.

7.3. Celastrol

Tripterygium wilfordii Hook F, a Chinese herbal medicine for expelling rheumatism, has the functions of expelling wind and dampness, promoting blood circulation and dredging collaterals, reducing swelling and pain, killing insects, and detoxifying. Modern studies have shown that it has anti-inflammatory, immunosuppressive, anti-fertility, anti-tumor, antibacterial, and pain-relieving effects, but it is not widely used in clinical practice due to its high toxicity and side effects [37]. Celastrol as one of the main active ingredients of the Chinese herbal medicine Tripterygium wilfordii Hook F, recent studies have found that celastrol has good pharmacological effects such as anti-inflammation, anti-oxidation, immunosuppression, anti-tumor, anti-obesity, and anti-neurodegenerative diseases. Liu [38] explored the effect of tripterygium wilfordii on the expression of Notch signaling pathway in the kidney tissue of rats with IgA nephropathy. The results showed that Notch1, Jagged1, Hes1, The expression of Hey1 was significantly increased, and the hematuria and 24h urine protein in IgA nephropathy rats were significantly decreased after the intervention of

tripterine, and the expressions of Notch1, Jagged1, Hes1, and Hey1 in kidney tissue were significantly decreased. This proves that tripterine can reduce the generation of hematuria and proteinuria by inhibiting the expression of Notch signaling pathway in the kidney tissue of IgA nephropathy rats, thus playing a therapeutic role in rat IgA nephropathy.

7.4. Resveratrol

Resveratrol exists in a variety of plants, and a large amount of resveratrol can be extracted from Polygonum cuspidatum, Polygonum multiflorum, Cassia, Mulberry, Lily, etc. Studies have found that resveratrol has antibacterial, anti-tumor, anti-inflammatory, anti-allergic, hypolipidemic, anti-oxidant, anti-free radical and other pharmacological effects [39]. Resveratrol can play an anti-fibrotic effect on the lung, liver, kidney, heart and other organs through different pathways and different molecular levels, by reducing the accumulation of macrophages and down-regulating IL-6, intercellular adhesion molecule 1, and monocytes Expression of chemoattractant protein 1 exerts anti-renal fibrosis effect [40]. Yu [41] found that the expressions of IL-6, IL-1β, TNF-α, creatinine, urobilin, 24h urine protein, IgA deposition, Notch1 and Jagged1 proteins in the serum of rats in the IgA nephropathy model group increased, and white The expressions of the above indicators were significantly decreased in the resveratrol group and the losartan group, and the difference between the resveratrol group and the losartan group was not statistically significant. It shows that resveratrol can reduce inflammatory response and IgA deposition, and inhibit the transduction of Notch signaling pathway, and protect the renal function of rats with IgA nephropathy.

The above studies have shown that the protective effect of traditional Chinese medicine on renal fibrosis in IgA nephropathy can inhibit the inflammatory response, reduce glomerular damage, and reverse the process of renal fibrosis by regulating the expression of genes downstream of the Notch signaling pathway or regulating the modification of related proteins. Improve the renal function of patients with IgA nephropathy, reduce symptoms such as proteinuria and hematuria, and delay the development of the disease. The role of traditional Chinese medicine in regulating the Notch signaling pathway in kidney diseases has potential clinical application prospects. Traditional Chinese medicine has shown potential curative effect in the treatment of IgA nephropathy by regulating the Notch pathway. However, due to the lack of single Chinese medicine and traditional Chinese medicine compound, there are few studies on the ingredients of Chinese medicine, and the Notch signaling pathway is only limited to Notch1 and Jagged1. Protein research lacks more data support from large-scale, multi-center experiments. Future research should further clarify the mechanism of action of traditional Chinese medicine on the Notch pathway, and carry out more clinical studies to verify its efficacy and safety, so as to strengthen the role of traditional Chinese medicine in the treatment of kidney diseases.

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