The Research Progress of PDGF-C/PDGFR-α Signaling Pathway in Renal Fibrosis and its Traditional Chinese Medicine Intervention

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Abstract: Traditional Chinese Medicine (TCM) is a valuable heritage of human experience [1]. Salvia (dan shen) is one of the most widely used herbs in TCM for treating kidney diseases. Whereas, Salvianolic acid A, B and C are Salvia's important component. The component compatibility of them for renal fibrosis is a doable and innovative proposition. The literature describing intervention effect of compatibility of Salvia miltiorrhiza water-soluble active components on PDGF-C/PDGFR-α signaling pathway in renal fibrosis. The summary of renal fibrosis, the etiology and pathogenesis of PDGF-C/PDGFR-α signaling pathway and the development in the research of TCM intervention were all examined. PDGF-C and PDGFR-α contribute to the formation of the renal cortical interstitium. Almost all experimental and human renal diseases are characterized by altered expression of the PDGF-C/PDGFR-α signaling pathway. Accordingly, component compatibility of TCM is an effective treatment for renal fibrosis, which is a most innovative application. It can improve renal function, renal tubular function and kidney pathology both in animal experiments and cell culture. Accordingly, it probably has a certain protective effect to the kidney.

Keywords: Renal fibrosis, PDGF-C/PDGFR-α signaling pathway, Traditional Chinese medicine.

INTRODUCTION

Renal fibrosis is the basic pathological change and general way of all kinds of kidney disease progression. Extra cellular matrix gather in the renal interstitial, kidney tissue's destruction of structure and loss of function. In all kinds of kidney disease, cell signaling pathways lead to renal fibrosis with excessive expression of cytokines. The previous researches mainly concentrated on transforming growth factor-β/Smad signaling pathway, mitogen-activated protein kinases cascade signaling pathway and adenosine pathway and so on. Recent study shows that PDGF-C/PDGFR-α signaling pathway may also play an important role in renal fibrosis. Thus, it may be a new target for prevention and treatment of renal fibrosis through restraining PDGF/PDGFR signaling pathway.

The TCMs including Astragalus (Radix Astragali, huang qi) and Salvia are widely used in the prevention and treatment of renal fibrosis. Pathogenesis of renal fibrosis tip: kidney collateral stasis is one of the key pathogenesis of renal fibrosis. Therefore, TCM for renal fibrosis pathogenesis, through promoting blood circulation and removing blood stasis, cooling blood and eliminating carbuncle play function. This paper summarizes such progresses of PDGF-C/PDGFR-α signaling pathway in renal fibrosis and its traditional Chinese medicine intervention.

THE SUMMARY OF RENAL FIBROSIS

Chronic kidney disease (CKD) has become a worldwide health and social problem [2]. Renal fibrosis is a characteristic feature and pathological basis for all forms of CKD progress to end-stage renal disease. Fibrosis can be considered as wound healing that never ceases. In the setting of tissue repair, myofibroblasts appear in conjunction with inflammatory response to provide the required physical and biochemical support to enable regeneration, upon which all repair activities come to a halt with the disappearance of activated myofibroblasts and inflammation [3]. Deposition of pathological matrix in the interstitial space and within the walls of glomerular capillaries as well as the cellular processes resulting in this deposition are increasingly recognized as important factors amplifying kidney injury and accelerating nephron demise. Recent insights into the cellular and molecular mechanisms of fibrogenesis herald the promise of new therapies to slow kidney disease progression, cell signaling pathway is one of them [4].

PDGF-C/PDGFR-α SIGNALING PATHWAY

Platelet-derived growth factor (PDGF) comprises a family of homo- or heterodimeric growth factors, namely, PDGF-AA, -AB, -BB, -CC, and –DD. They

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belong to a family of structurally and functionally related growth factors, including the vascular endothelial growth factors, and are highly conserved throughout species. After being first described as a serum growth factor for fibroblasts and smooth muscle cells, human PDGF was discovered about three decades ago as a disulfide-linked dimer of polypeptide chains A and B [5-6]. PDGF-C and -D were identified more recently and in contrast to PDGF-A and -B are secreted in a latent form with an N-terminal CUB (complement C1r/C1s, Uegf, Bmp1) domain, which has to be extracellularly cleaved before these ligands can bind and activate their receptors. Tissue-type plasminogen activator (tPA) and plasmin are identified PDGF-CC-activating proteases, whereas PDGF-DD is activated by urokinase-type plasminogen activator (uPA) and matriptase (MT-Sp1). All isoforms bind to two tyrosine kinase receptor chains, which are combined to the homodimeric PDGF-receptor (PDGFR)-αα and –ββ and the heterodimeric receptor PDGFR-αβ, with different binding specificities and affinities. Upon ligand binding, PDGF receptors dimerize, possess tyrosine kinase activity, and get autophosphorylated [7].

The localization of PDGF isoforms and their receptors in normal postnatal human and rodent kidneys has been well described. Above all, we have detected an upregulated expression of PDGF-C in fibrotic interstitial areas in murine, rat, and human kidney fibrosis. PDGF-C has been localized to arterial smooth muscle cells and collecting-duct epithelial cells in the rat. In humans, PDGF-C is expressed by parietal epithelial cells in the glomerulus, by tubular cells from all parts of the nephron distal to the proximal tubules, and by arterial endothelial cells. Explicitly at sites of tubulointerstitial fibrosis there is an upregulated expression of PDGF-C by interstitial cells and macrophages, which localize near areas with increased PDGFR-α expression, e.g., in smooth muscle cells and myofibroblasts. Glomerular infiltrating PDGF-C expressing macrophages in experimental lupus nephritis have been shown to be important for crescent formation [8]. PDGF-C was also upregulated in mesangial cells and podocytes upon cellular injury in different animal models and in human renal biopsies [9]. In experimental kidney fibrosis induced by UUO, kidneys from PDGF-$C^{-/-}$ mice showed a nonsignificant trend toward decreased PDGFR-α mRNA expression in comparison to WT littermates on day 5 after disease induction [10]. Also, Chen and colleagues demonstrate that altered PDGF/PDGFR signaling is associated with kidney fibrosis, and provide compelling evidence for the role of PDGFR signaling in myofibroblast activation [11].

Explicitly, upregulated renal expression and de novo expression of PDGF isoforms and their receptors have been observed in nearly all analyzed rodent-kidney injury models and also in the corresponding human renal diseases. Hereby, we speculate that specific PDGF-C neutralization significantly reduced the development of unilateral ureteral obstruction (UUO) induced fibrosis and inflammation in the kidney. Although more studies are required, there is no doubt that endogenous inhibitors of PDGF-C/PDGFR-α signaling pathway is a new target for prevention and treatment of renal fibrosis.

TRADITIONAL CHINESE MEDICINE INTERVENTION (TCM)

The TCM is widely used in the prevention and treatment of CKD including Astragalus and Salvia and so on [12]. Plenty of clinical trials has indicated that a variety of TCMs could effectively prevent chronic renal failure, and was widely used in the clinical practice. For example, several small clinical studies published in Chinese language journals suggest that Astragalus decreases proteinuria and improves the plasma levels of total cholesterol and albumin in patients with nephrotic syndrome. In a systematical review of randomized and semirandomized trials using Astragalus for the treatment of diabetic nephropathy, 21 randomized controlled and 4 case–controlled studies with a total of 1804 patients (945 in the treatment group and 859 in the control group) were included. The authors of the systematic review concluded that Astragalusis able to improve renal function and reduce proteinuria in patients with diabetic nephropathy [13].

However, studies on mechanism were still nearly blank, which may prevent further improvement of therapeutic efficacy. Recent researches show that Salvia is a biological pattern on the application of TCM. It can be used as a reference and templet for other TCMs. Related studies about the Salvia miltiorrhiza water-soluble active components have demonstrated that [14], water-soluble active components from salvia miltiorrhiza including Salvianolic acid A, B and C, have strong antioxidant activity and antithrombotic effect by scavenging oxygen free radicals and inhibiting lipid peroxidation reaction. Pathogenesis of renal fibrosis tip: kidney collateral stasis is one of the key pathogenesis

of renal fibrosis. Therefore, Salvianolic acid A, B and C component compatibility for renal fibrosis pathogenesis (At home and abroad has not been reported in the literature), through promoting blood circulation and removing blood stasis, cooling blood and eliminating carbuncle play function. What's more, by our research group's early experiment running [15], results show that component compatibility of Salvianolic acid A and B could reduce the development of UUO induced fibrosis and inflammation in the kidney, its mechanism may be related to the intervention of PDGF-C/PDGFR-α signaling pathway.

DISCUSSION

CKD affects increasing numbers of people around the world, but as yet, effective strategies to control its progression have not been universally accepted [16]. A variety of signaling pathways involved in the process of renal fibrosis, which is one of the main pathological features of CKD. All four PDGF isoforms and their receptors are expressed early during kidney development, which was reviewed in detail elsewhere. Most data demonstrating the important, largely indispensable, roles of PDGFs for renal development came from mice deficient for single PDGF isoforms or receptor chains. PDGF-A,-B,-C, PDGFR-β- or PDGFR-α- knockout mice all die in the prenatal period or early during postnatal life. For PDGF-C knockouts, this phenotype depends on the genetic background [17]. PDGFR-α is widely expressed by renal interstitial cells and constitutively to some degree by mesangial cells and smooth muscle cells of the renal arterial vasculature. Studies in mice support a distinct role of PDGFR-α agonist PDGF-C for the development of tubulointerstitial fibrosis [17]. Accordingly, mice with UUO-induced renal fibrosis treated with a specific neutralizing anti-PDGF-C antiserum exhibited a striking reduction of tubulointerstitial fibrotic lesions, a remarkable reduction of interstitial myofibroblast accumulation, and a decrease in leukocyte infiltration. Recent data also demonstrated the potent proangiogenic role of PDGF-C for the glomerular endothelium [18]. PDGF-C infusion accelerated glomerular capillary repair in the early mesangiolytic phase of mesangioproliferative glomerulonephritis in rats, whereas specific antagonism of PDGF-C in this model and in a mouse model of thrombotic microangiopathy blocked restoration of the glomerular endothelium. In conclusion, intervention of PDGF-C/PDGFR-α signaling pathway is feasible. Furthermore PDGF-C is a recently identified cytokine that acts via the PDGF-receptor and is a potent mitogen for human fibroblasts and vascular smooth muscle cells *in vitro*. Observations in different organs suggest that PDGF-C plays an important role in the regulation of fibrosis [19]. In addition, component compatibility of TCM had an advantage in treating renal fibrosis, which is a most innovative application.

The existing problems in renal fibrosis research currently are as follows: firstly, the specific regulation of many new discoveried signaling pathways is unclear; secondly, research work is confined to a single signal pathway and failed to involved in their interweaving; thirdly, many researches just focus on animal experiments and cell culture, how to guide it to clinical drug application still remain to be solved. Based on a literature review, development of renal fibrosis is a consequence of combined action of a multi-factor, multiple-link and many signaling pathways.

However, there are still several problems among these studies. Well-designed animal studies and randomized clinical trials are needed to validate the physiological and pathological roles of these agents for treatment of patients with renal fibrosis. Further rigorous studies could provide more evidence for us to use the component compatibility of TCMs for the treatment of renal fibrosis, which is a huge innovation both to the patients and the healthcare system.

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