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Review Article

IL-17 AND KIDNEY DISEASE

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ABSTRACT

IL-17（Interleukin 17）is secreted by helper T lymphocyte 17 (Helper T lymphocyte17 Th17), a recently discovered class of $CD4^+$T lymphocytes that are distinct from Th1 and Th2 cells. Phenotypically distinct T lymphocytes have different capabilities for differentiation and regulation, and among them, Th17 cells are named for their characteristic secretion of interleukin 17 (IL-17). It has been shown that Th17 cells and their secreted IL-17 are involved in the development of diseases such as infections, autoimmune diseases, allergic diseases, tumors, and transplant rejection by mediating inflammatory responses. The relationship between IL-17 and renal diseases is reviewed in order to gain a deeper understanding of the pathogenesis of renal diseases and to provide a basis for finding new targets and new therapeutic strategies for the diagnosis and treatment of renal diseases.

Keywords: Interleukin 17;T helper 17 cells;Cytokine;Kidney disease.

INTRODUCTION

Th17 cells are a recently identified subpopulation of CD4+ T cells that secrete cytokines such as IL-17 (interleukin-17,IL-17), and the Th17/IL-17 axis is mainly characterized by effector and pro-inflammatory functions that are involved in the pathogenesis of many immune-mediated diseases. receptors of the IL-17 family (IL-17RA, IL-17RC, and IL-17RE) are expressed in most kidney-associated cells (podocytes, tubular epithelial cells, thylakoid cells and renal endothelial cells) and are involved therein in promoting a pro-inflammatory environment that disrupts the morphology and function of the renal unit, which in turn leads to loss of function of the associated organ. This article reviews the progress of research on IL-17 and its related factors in renal diseases.

DISCUSSION

Th17/IL-17 axis:

Introduction to Th17:

Th17 cells differentiate from initial T helper cells in the presence of IL-1β, IL-6, IL-23 and TGF-β, which are key cytokines for their differentiation and require the spectrum-specific transcription factor class retinoid-related orphan receptor-γ (RORγt). Mature APCs (after binding of DAMPs to TLRs) trigger lymphocyte activation through the interaction of MHC II with TCR and several costimulatory molecules[1]. In the context of this interaction, mature APCs produce key cytokines for Th17 differentiation, using nuclear factor kappa B (NF-κB) and/or mitogen-activated protein kinase (MAPK) as signaling pathways. These cytokines bind to their respective receptors in CD4+ T cells and trigger a series of downstream events involving signal transduction and activator of transcription 3 (STAT3), which stimulates the synthesis of IL-17 and IL-21 by binding directly to them.

Erythropoietin (EPO) attaches its receptor (EPO-R) to CD4+ T cells, directly inhibits TH17 production and promotes the transdifferentiation of TH17 to IL-17-FOXP3+CD4+ T cells[2], which are induced into different T cell subpopulations when primary CD4 ten T cells (Th0) receive different cytokines and stimulatory effects, such as IL-12 induces Th0 to differentiate into Th1 cells, IL-4 induces Th2 cell polarization, transforming growth factor-β (TGF-β) induces the production of regulatory T cells (Rygulatory cell, Treg) cells through the transcription factor Foxp3 pathway, and Th0 is induced by TGF-β and Th0 differentiates into Th17 cells through the transcription factor solitary nuclear receptor (RORγt) signaling pathway under the combined action of TGF-β and IL-6. When RORγt gene expression is lacking, the presence of Th17 can still be detected, which indicates that other relevant transcription factors exist in the differentiation of Th17 cells, and when IL-6 is lacking, IL-21 in concert with TGF-β can promote the conversion of CD+ T cells to Th17 differentiation process is divided into three stages: induction of differentiation, expansion and stabilization. Th17 cells highly express IL-23R and chemokine receptor 6 (CCR6) and CCR4 on the surface, and IL-1β, IL-6 and IL-23 promote the differentiation of human Th17 cells, which further indicates that IL-23 is one of the important factors to maintain the phenotype of Th17 cells. In contrast, IL-27, IL-4 and γ-interferon (IFN-γ) have inhibitory effects on Th17 cell

differentiation. In the kidney, dendritic cell-derived IL-23 acts on γδ T cells to promote IL-17A-mediated renal inflammation, while Th17 cell-produced IL-17A stimulates renal tubular cells to express CXCL5 and CCL20, thereby recruiting neutrophils and enhancing Th17 cell infiltration[3].

Biological role of Th17/IL-17:

Th17 plays an important role in host defense against extracellular pathogens and fungal infections, and Th17 and its secreted cytokines play an important role in tissue inflammation and the development of autoimmune diseases, Th17 cells secrete IL-17A-F, IL-21 and IL-26. The main pathway for IL-17 production, but other cells can also produce IL-17, such as neutrophils, mast cells, and mesenchymal cells. Interleukin-17 (IL-17A, also known as CTLA-8) has a family of six cytokines: IL-17A (IL-17), IL-17B, IL-17C, IL-17D, IL-17E (IL 25) and IL-17F, which plays an important role in tumor progression.The IL-17R family includes five receptor subunits: IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE.IL-17 and IL-17F can exist either as homodimers or as heterodimers and are expressed through the dimeric IL-17RA and IL-17RC receptor complexes to transmit signals. Although IL-17R is widely expressed, non-hematopoietic cells are usually the primary responders to IL-17. Upon ligand binding, the bridging protein Act1 is recruited to the receptor subunit and activates multiple cellular signaling pathways via distinct TNF receptor-associated factor (TRAF) proteins.IL-17 has potent inflammatory effects. It promotes the production of growth factors as well as chemokines and has a synergistic effect with cytokines such as IL-6 to amplify the local inflammatory response, and it has a role in recruiting neutrophils to local sites of inflammation, thus further enhancing tissue immune damage.IL-17C promotes the response of T17 cells and facilitates the expression of IL-17RE on immune-mediated CD4 T17 cells[4], Th17 cells belong to CD4 deca-T cells, which play an important role in the pathogenesis of autoimmune diseases, transplant rejection, etc. Abnormal expression of IL-17 is closely associated with chronic inflammatory diseases, autoimmune diseases, and transplant rejection.

Plasticity of Th17:

Recent studies suggest that Th17 cells have plasticity, that is, the ability of The17 to regulate various functions by changing itself under certain conditions, such as: maintaining the balance between cytokines and Treg and Th17, and in the Foxp3Treg cell pool, Foxp-RORrtT lymphocytes can be transformed into Foxp3+IL-17T lymphocytes, which can also further demonstrate the pro-inflammatory role of Treg cells, and there are relevant experiments demonstrating the limited plasticity of Th17 in acute and chronic glomerulonephritis models. In genetic studies, Tbx21 and Cata3 were found in Th17, and Tbx21 and Cata3 are transcription factors of Th1 and Th2, which also indicates that Th17 converts their functions under certain conditions.

IL-17 and glomerular disease:

Anti-glomerular basement membrane (GBM) nephritis:

Anti-glomerular basement membrane (GBM) nephritis is a rare autoimmune disease that is characterized by the presence of circulating antibodies against the basement membrane (GBM) and the deposition of related antibody immune complexes in the glomerular basement membrane. The role of T cells

in the pathogenesis of the disease has also been identified and emphasized, with the involvement of TGF-β1 in the differentiation process of both Treg and Th17, as well as studies showing that Treg can be converted to Th17 under certain conditions. The idea that IL-17A signaling pathway is involved in anti-GBM GN was first proposed in the nephrotoxic serum nephritis NTT study, in which Th17-mediated immune damage was predominant in the early stage of anti-GBM nephritis, while regulatory T cells (Treg), a specific subpopulation of T cells, reduced the disease by suppressing T cell immune response, attenuating pathological damage and playing a protective role in anti-GBM nephritis. By comparing the infiltration of Th17 cells in IL-23p 19,IL-17 gene-deficient mice and in a mouse model of wild-type nephropathy, the former was less severe than the latter[5].

IgA nephropathy:

IgA nephropathy (IgAN) is a type of primary glomerulonephritis in which immunopathology of renal biopsies shows IgA-dominated immune complex deposition in the glomerular thylakoid region. The level of IL-17 in the urine of patients with IgAN is higher than that of healthy controls, and urinary protein excretion is positively correlated with IL-17 excretion[6]. In patients with IgA nephropathy, serum IL-17 and IL-6 are elevated but IL-10 is decreased, serum IL-17 is positively correlated with their 24h urine protein, urinary IL-17 is negatively correlated with glomerular filtration rate, peripheral blood Th17 in IgA patients is positively correlated with IL-17, and IL-17 is positively correlated with the degree of thylakoid cell proliferation, IL-17 can further aggravate the renal inflammatory response. Respiratory syncytial virus (RSV) infection may increase IL-17 levels by promoting CD4 T-cell production in human glomerular thylakoid cells by promoting CD4 T-cell proliferation.C5a stimulation enhances these pathological behaviors and C5aR1 inhibition attenuates them[7], and stimulation of human thylakoid cells with IgA1 in vitro has been shown to induce IL-17 production[8]. IL-17 may be involved in the development of nephropathy by inducing IgA1 production and glycosylation in B cells[6], and stimulation with a certain concentration of IL-17 causes the degree of IgAN glycosylation to increase with time, which further aggravates the degree of kidney injury and tissue fibrosis, and application of immunofluorescence staining in the kidneys of IGAN patients with CCR6+IL-17+ T lymphocytes were shown to be present, while not found in control kidneys[6], which provides a possible new therapeutic strategy for targeting Th17,IL-17 antagonists for the treatment of IgAN.

IL-17 and anti-neutrophil cytoplasmic antibody (ANCN)-associated nephritis:

ANCA-associated vasculitis (AAV) is a general term for a group of diseases involving renal injury, and experimental animal models and clinical trials have demonstrated that Th17 and IL-17 are key mediators of renal tissue injury in models of renal immune-mediated disease[10], and in patients with ANCA-associated nephritis or lupus nephritis, the Serum IL-17 levels correlate with disease activity[11], however, the role played by IL-17 in human anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis is unclear,Assays in patients not receiving immunosuppressive therapy suggest a positive correlation between serum creatinine levels and renal tubulointerstitial IL-17,The establishment of an anti-myeloperoxidase (MPO) vasculitis model in In this model, IL-17 was found to promote the recruitment of neutrophils to the glomerulus,

which would enhance the response of acquired immunity to MPO and lead to the exacerbation of glomerular vasculitis, in which neutrophils and mast cells play a role, especially neutrophils.

IL-17 and primary nephrotic syndrome (PNS):

Primary nephrotic syndrome (PNS) is a primary glomerular disease with altered glomerular basement membrane permeability due to immune dysfunction, especially T-lymphocyte dysfunction, and is one of the most common chronic kidney diseases in childhood, which is clinically treated with glucocorticoids. 17 may cause kidney injury by inducing a local inflammatory waterfall response. Some experiments have illustrated that IL-17 exacerbates the progression of nephrotic syndrome through damage to podocytes[12]. A clinical study showed that the level of IL-17 was much higher in serum specimens from adult patients with PNS than in healthy subjects, and analysis of different types of primary nephrotic syndrome concluded that IL-17 did not correlate significantly with tissue typing and may play a key role in promoting the inflammatory response during tissue injury, with an increased proportion of peripheral blood Th17 cells in children with PNS and an expression of IL- in peripheral blood mononuclear cells The percentage of peripheral blood Th17 cells and the expression of IL-17 and IL-23 by peripheral blood mononuclear cells increased in children with PNS, while the serum and urine levels of IL-17 in children with PNS were positively correlated with proteinuria levels during the relapse period. Clinical experiments in patients with nephrotic syndrome (SSNS) suggest a positive correlation between IL-17 concentration and 24-hour urine protein before treatment, and a positive correlation between the decrease in 24-hour proteinuria and the decrease in IL-17 concentration after treatment in SDNS.

IL-17 and lupus nephriti (LN):

LN is a group of autoimmune diseases involving kidney damage in systemic lupus erythematosus (SLE) and is one of the signals suggesting a poor prognosis in SLE. The potential pro-inflammatory role of IL-17 in lupus nephritis has been demonstrated in animal experimental models[13]. Histologically, it has been suggested that Th17 cells in peripheral blood and IL-17 levels in serum correlate significantly with renal biopsy classification in LN and that there is a significant positive correlation between serum IL-17 levels and nephritis activity index [1], and samples were collected from patients with LN or glomerulonephritis and healthy controls, and the number of IL-17 NKT cells and IL-17 expression levels were found to be elevated in the blood and kidney of LN patients, respectively. 17 expression levels were elevated, respectively, and some experiments confirmed the involvement of natural killer T (NKT) cells in the pathogenesis of LN[14]. Plasma IL-17 was significantly elevated in patients with lupus nephritis compared to the non-nephritic group of SLE[15], and high levels of IL-17 predicted poorer histopathological outcomes in LN patients treated with immunosuppressive therapy, and IL-17-producing double-negative T cells were detected in nephritic kidneys of MRL/LPR mice and lupus patients, and IL-17 cytokines and their signaling through the junction protein Act1 signaling in a lethal pathological role in FcgR2b-deficient lupus nephritis mouse model[16], and studies in autoimmune-prone Bxd2 mice suggest that IL-17 and Th17 cells coordinate the formation of autoreactive germinal centers leading to lupus-like disease.DNT cells are an important source of renal IL-17 in MRL/lpr mice, IL-23 receptor-deficient

lupus-prone B6/lpr and MLR/lpr mice exhibited improved lupus nephritis with reduced DNT cells and IL-17A-producing cells, and although IFN-γ has also been reported to play a role in experimental models of lupus nephritis, the group expressed IL-17a- and IL-17a-producing cells extensively in MRL/lpr and NZB/NZW lupus models. IFN-γ-producing cells, showing a highly pathogenic role of IFN-γ. Anti-IFN-γ treatment reduced the severity of experimental lupus nephritis, whereas IL-17A deficiency or anti-IL-17A treatment had no significant effect on the clinical course[17], and the number of Th17 cells in the peripheral blood of lupus patients was elevated during the exacerbation of the disease and decreased after successful treatment. Another study showed that plasma IL-17 levels were positively correlated with proteinuria and dsDNA antibody levels in patients with lupus nephritis, suggesting that IL-17 could be used as a biomarker of disease activity. Interestingly, we observed a negative correlation between Th17 cell frequency and type I interferon levels in a subgroup of lupus patients. In contrast, another study found no significant association between serum IL-17 levels and nephritis in lupus patients[18]. Thus, the functional role of IL-17 or IL-17-producing innate and acquired immune cells in the renal involvement of lupus patients remains to be fully elucidated.

IL-17 and diabetic nephropathy:

Diabetic nephropathy (DN) is one of the most common chronic complications of diabetes mellitus (DM) and a major cause of end-stage renal failure, and with the in-depth studies in recent years suggesting that immune factors play a considerable role in the pathogenesis of type 1 diabetes mellitus (T1DM), the role of individual cytokines in disease progression is not fully understood. diabetes mellitus,T1DM) the immune landscape is extremely complex and the role of individual cytokines in disease progression is not fully understood, IL-17 has the potential to serve as new evidence of an influential factor affecting diabetic complications in distal tissues[19], chronic perfusion of angiotensin II stimulates IL-17 production and increases IL-17 expression within the vessel wall . Exogenous IL-17 increases hypertensive responses and endothelial dysfunction by stimulating the Rho kinase pathway.IL-17A attenuates renal inflammation and fibrosis by regulating autophagy or macrophage phenotype[20]. Targeting IL17A but not IL-17F deficiency or blockade reduces elevated blood pressure and renal inflammation in patients with angiotensin II-dependent hypertension[21].In in vitro studies, IL-17 in combination with IL-1β and interferon (IFN)-γ led to human islet β-cell death, and IL-17 prompted the expression and secretion of pro-inflammatory chemokines in human islet cells, and it was found that IL-17A and IL-17F gene expression levels were significantly increased in peripheral blood mononuclear cells (PBMCs) of children with T1DM, and it was shown that serum IL-17 was significantly elevated in the higher glucose group of T1DM patients compared to normal controls, while there was no significant difference between serum IL-17 in the lower glucose group and normal controls[22], and IL-17 deficiency improved blood glucose and secretion in non-obese diabetic (NOD) mice, IL-17 deficiency delays the onset of diabetes in NOD mice[23], but at the same time some studies have come to a different conclusion, IL-17 does not increase the chance of developing diabetes in NOD mice, and serum IL-17 levels in T1DM patients are not significantly different from normal controls[24], however, type I diabetic mice genetically deficient in However, the genetic deficiency of IL-17A in type I diabetic mice can develop more severe

nephropathy[25], and the decrease of IL-17A level can exacerbate the production of proteinuria, and the increase of IL-17 level in type I diabetic mice can protect the podocytes and renal tubular cells, thus reducing the inflammation and fibrosis in the kidney of DN mice[26]. Type 2 diabetes mellitus (T2DM) T2DM patients have significantly higher IL-10 and IL-17 producing CD3+ T lymphocytes in peripheral blood[27], however, it has also been shown that serum IL-17 levels are not significantly different in T2DM patients without diabetic complications and with disease duration less than 5 years compared to normal controls[24]. In recent years, the relationship between IL-17 and DN pathogenesis has received increasing attention, and some clinical studies have suggested that IL-17A levels are elevated in the kidney tissue of patients with diabetic nephropathy and are positively correlated with decreased glomerular filtration rate[28]. IL-17 expression, glomerular thylakoid sclerosis and tubulointerstitial fibrosis were significantly reduced after intervention with the immunosuppressant rapamycin[29], while other studies have demonstrated a protective effect of IL-17 on the kidneys of DN mice, and the absence of IL-17 signaling was protective against streptozotocin-induced diabetic nephropathy, thus suggesting a pro-inflammatory role of IL-17 in its pathogenesis[30], and some studies suggest that renal injury is exacerbated after IL-17A knockout, while when treated with low doses of IL-17A, it reduces urinary protein and attenuates glomerular and interstitial fibrosis[25]. Proteinuria is both an early marker of DN and a response to podocyte injury, and in DN, a decrease in the number of podocytes correlates with the degree of proteinuria and is a strong predictor of eventual disease progression[30]. Taken together, these studies indicate that the exact role of IL-17 in the pathogenesis of DN is not yet clear.

IL-17 and kidney transplantation:

Kidney transplantation is one of the effective means of treating end-stage renal disease, and acute rejection is the most common complication after kidney transplantation, and early acute rejection is one of the important risk factors affecting the long-term survival and failure of the transplanted kidney.With the continuous research on organ transplantation immunity, more and more data have confirmed the involvement of IL-17 directly or indirectly in cellular and humoral immunity in the occurrence[31], and in studies IL-17 was found to have a possible role in promoting fibroblast proliferation in addition to inflammatory cell infiltration[32], and IL-17A gene expression levels were significantly higher after transplantation in recipients who experienced acute rejection (AR) than in controls[33], and IL-17 was found to increase in post-transplantation serum on day 3 after surgery in a mouse animal model, with the most pronounced increase on day 7[34]. type AA and A allele on IL-17F gene 7489A/GSNP may be associated with a lower risk of acute rejection and longer graft survival[35], and the level of IL-17 in the transplanted kidney was positively correlated with the degree of rejection. Some studies have shown that only few Th17 cells are infiltrated in the transplanted kidney, and IL-17+ cells are increased and are mainly neutrophils or mast cells, with few IL-17+ lymphocytes[36], and for patients receiving pretreatment with higher plasma levels of IL-17, perhaps the level of IL-17 can be measured as a predictive indicator for the early diagnosis of acute rejection, with clinical studies illustrated that in both graft kidney function stabilization (SGF) and graft kidney function rejection (RX), IL-17 levels were much higher in the RX group than in the SGF group after the 6th month of kidney transplantation[37],

IL-17 levels were much lower in the chronic rejection group than in the non-chronic rejection and uremic groups, IL-17 and IL-21 levels were found to be significantly higher in the graft kidney tissue of patients with graft kidney failure due to chronic rejection and IL-21 promoted lymphangiogenesis, which would accelerate the development of chronic rejection in transplanted kidneys.Since there are fewer studies on IL-17 cells in acute rejection of human kidney transplants, a large number of studies are needed to confirm the role of IL-17 cells in acute rejection of human kidney transplants.

CONCLUSION

IL-17 is the latest cytokine secreted by Th17 cells discovered in recent years, and it has been proved that IL-17 plays a key role in the development of inflammatory diseases, but its pathogenesis in autoimmune diseases and renal diseases is unknown, so the clinical diagnosis and treatment of related diseases are greatly limited. The sensitivity and specificity of cytokine levels for the diagnosis and treatment of kidney diseases provide a new direction for targeted therapy.

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