

TGF- β Study on the Role of Iron Death Signal Transduction in Diabetes Nephropathy

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Abstract: DN (Diabetes Nephropathy) is the result of multiple factors, and its pathogenesis is complex. Extensive evidence has proven TGF- β . It plays an important role in the pathogenesis of DN, but the specific way of action is still unclear. TGF- β after binding and activating its receptor, its signal transmission needs to be carried out by a series of post receptor signal molecules TGF- β . It is the last and common important mediator of kidney damage caused by changes in biochemical factors and cytokines, such as blood glucose rise in diabetes. It can directly lead to DN characteristic pathological changes such as renal cell hypertrophy, excessive accumulation of extracellular matrix, glomerulosclerosis, renal interstitial fibrosis, etc. In DN, TGF- β the characteristic function of the β - lactamase is to stimulate the matrix deposition in the mesangial region. Through TGF- β . Further study on the role of DN iron death signal transduction in diabetes islets β the research on the mechanism of cell injury is reviewed. At the same time, it can not only increase the synthesis of extracellular matrix, but also inhibit the degradation of extracellular matrix components.

1. Introduction

DN is one of the most serious and common chronic complications of diabetes and one of the main causes of end-stage renal failure. The basic pathological changes are glomerular and renal tubular hypertrophy, accumulation of extracellular matrix, thickening of basement membrane and glomerulosclerosis. DN is the result of multiple factors, and its pathogenesis is complex. A large amount of evidence has proved that TGF- β plays an important role in the pathogenesis of DN, but the specific way of action is still unclear. After TGF- β binds to and activates its receptor, its signal transmission needs a series of post-receptor signal molecules. Studies have shown that Smad protein is the only known intracellular kinase substrate of TGF-B receptor, which mediates intracellular signal transduction of TGF-B [1]. TGF- β is the last and common important mediator of kidney injury caused by some biochemical factors such as blood glucose elevation and cytokine changes in diabetes. It can directly lead to kidney hypertrophy, excessive accumulation of extracellular matrix, glomerulosclerosis, renal interstitial fibrosis and other DN characteristic pathological changes. In DN, the characteristic function of TGF- β is to stimulate matrix deposition in mesangial region. Although the signal transduction pathway of TGF- β through Smad family molecules regulating cell cycle has

been demonstrated in detail, the signal transduction pathway of TGF- β regulating mesangial matrix in one day is far from clear [2]. TGF- β cytokines produce various biological effects through different signal transduction pathways. TGF- β superfamily signals are transmitted from cell membrane to nucleus, and participate in and regulate various gene expressions.

There are countless components in the extracellular matrix, and the stimulation of matrix molecule synthesis and inhibition of its degradation can be regulated at various levels, so it is inferred that there are many signal transduction pathways involved. The key question is how TGF- β can coerce the stimulation response of various signal transduction pathways, and finally promote the deposition of extracellular matrix in mesangial area [3]. Iron death is a new form of cell death discovered in recent years, and it plays an important role in diseases. Many studies have shown that iron death may occur in the process of islet β cell injury. This article will review the current research on the mechanism of DN iron death in the process of islet β cell injury in diabetes [4]. At the same time, it can not only increase the synthesis of extracellular matrix but also inhibit the degradation of extracellular matrix components. Matrix metalloproteinase (MMP) is a key enzyme in the degradation of extracellular matrix, which can inhibit the activity of MMP. Iron death may be involved in the damage of islet β cells in DN, and it can find the target of inhibiting iron death, which may bring new methods and ideas for the treatment of DN [5].

2. Diabetes nephropathy

DN is one of the serious complications of diabetes patients, and its pathogenesis has not yet been fully understood. DN often leads to chronic renal insufficiency, accounting for about one-third of patients with end-stage renal disease. DN is a chronic disease that occurs when the glucose level in the blood increases because the human body cannot secrete or secrete enough insulin or cannot use insulin effectively [6]. The most important pathological change of DN is that the accumulation of ECM in the mesangial area leads to glomerulosclerosis, which is an important pathological basis for renal failure in diabetes patients. The process of visceral lesions is the result of the expression and regulation of multiple cytokines and growth factors in the whole body and kidney caused by high glucose. Among them, transforming growth factors play an important role. The basic pathological changes were hypertrophy of glomeruli and tubules, accumulation of extracellular matrix, thickening of basement membrane and glomerulosclerosis. The pathogenesis of DN is shown in Figure 1.

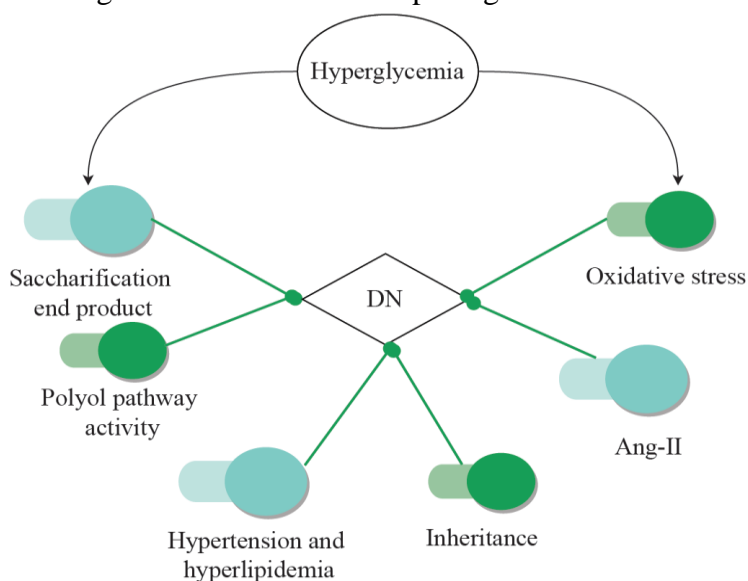


Figure 1: Pathogenesis of DN

DN is the result of multiple factors, and its pathogenesis is complex. EMT is found in the kidneys of interstitial fibrosis diabetes model mice and human kidneys, except for mesangial matrix deposition and blush scar formation. Vascular dysfunction plays an important role in early and late diabetic nephropathy. In the early stage of glycoferosis, there is often an increase in glomerular blood flow secondary to bulbar arteriolar dilatation. Excessive apoptosis of renal tubular epithelial cells in DN can affect the effective repair after renal injury and aggravate renal interstitial fibrosis [7]. Long term hyperglycemia can cause damage to the kidney, heart, blood vessels, eyes, nerves and other organs, causing a heavy burden on people's health. Therefore, DN is a serious health problem, which has reached a worrying level.

3. Iron Death and Diabetic Nephropathy

Iron death is a new type of cell death caused by iron-dependent oxidative damage glutathione, GSH) is exhausted, the activity of glutathione peroxidase 4 (GPx4) decreases, and lipid oxides cannot be metabolized by GSH reduction catalyzed by GPX4. Then ferrous ions oxidized lipids in a similar way to Fenton reaction to produce a large number of reactiveoxygenspecies (ROS), which promoted iron death in cells, thus playing an important role in cell injury [8]. It may be involved in the process of glomerular hypertrophy and renal tubular epithelial cells fattening in the early stage, and it may promote the deposition of extracellular matrix, accelerate glomerular sclerosis, renal tubular atrophy and interstitial fibrosis in the middle and late stage. A key feature of the death process of DN is the accumulation of iron-dependent lipid peroxide, which is usually removed by the antioxidant enzyme glutathione peroxidase 4. It is not difficult to imagine that glomerular microcirculation should be carried out at a high circulation level, and there should also be proliferation of mesangial cells.

However, the actual pathological state is manifested as the expansion of glomerular blood vessels, the activation of various molecules in mesangial matrix and the subsequent glomerular hypertrophy. It is found that iron death in DN is an important way of dopaminergic neuron loss, so inhibiting iron death can be a new method to treat Parkinson's disease. Tumor suppressor P53 can down-regulate SLC7A11, thereby inhibiting the uptake of cystine, Cys) by cells and causing iron death. The injury and loss of glomerular capillaries is also one of the factors that contribute to the formation of glomerulosclerosis, and the apoptosis of glomerular capillary endothelial cells has been proved. The down-regulation of SL7A11 eventually leads to the loss of intracellular cystine level and the subsequent depletion of glutathione biosynthesis, which indirectly leads to the inhibition of GPX4 activity and the subsequent activation of iron death. Therefore, SL7A11 is the key protein in the regulation of iron death. SLC7A11 has been proved to play an important role in many iron death models.

4. TGF- β the role of signaling pathway in iron death in diabetes nephropathy

4.1 Role in glomerulosclerosis

The damage and loss of glomerular capillaries is also one of the factors for the formation of glomerulosclerosis, which has been proved that TGF- β . It can induce apoptosis of glomerular capillary endothelial cells. Early TGF- β . It plays an important role in the proliferation, hypertrophy, apoptosis and local and systemic immune responses of glomerular cells, and its main role in the middle and late stages is to regulate ECM (extracellular matrix) metabolism [9]. Application of neutralizing anti TGF in db/db diabetes mice- β Monoclonal antibody can reduce the expression of collagen IV and fibronectin in the kidney, reduce the degree of glomerular basement membrane thickening and mesangial hyperplasia, improve glomerular filtration rate, and reduce the level of blood creatinine.

TGF- β the most important pathological change of signaling pathway and glomerulosclerosis DN is that the accumulation of ECM in the mesangial area leads to glomerulosclerosis, which is an important pathological basis for renal failure in diabetes patients. A large number of studies have confirmed that TGF- β . It can promote the synthesis and deposition of ECM, thus accelerating the process of glomerulosclerosis. Glomerulosclerosis is the common outcome of glomerular injury and pathological changes caused by various reasons, and also the main pathological basis of renal failure. The abnormal deposition of extracellular matrix of renal tubules in the glomerulus is the main lesion causing glomerulosclerosis [10]. TGF- β the signal transduction pathways are different in different types of cells; Moreover, the other phase effects that may be caused by these small co conduction pathways are complicated. Undoubtedly, it increases the complexity of the research work, as shown in Figure 2.

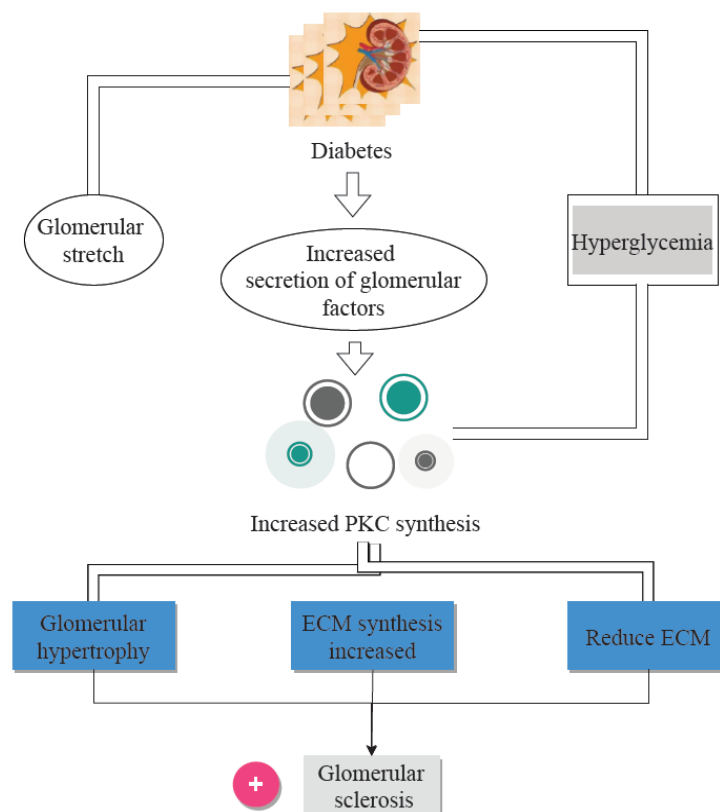


Figure 2: Role of TGF- β in DN iron death signal transduction

It is found that TGF- β causes diabetic iron death and glomerulosclerosis, which is mainly related to advanced glycation end products. TGF- β has various biological effects. For interstitial cells such as mesangial cells and fibroblasts, TGF- β has dual regulatory effects, with high concentration inhibiting cell proliferation and low concentration promoting cell proliferation. AGEs can increase the expression of vascular endothelial growth factor and vascular cell adhesion molecule -1 by binding to AGE receptor in glomerulus, which can promote the increase of mononuclear macrophages in glomerulus. By activating reactive oxygen species, cyclooxygenase and platelet activating factor, AGEs can increase TGF- β , resulting in mesangial hyperplasia, basement membrane thickening, glomerulosclerosis and proteinuria.

4.2 Role in renal interstitial fibrosis

The early pathological changes of DN are mainly glomerular hypertrophy and hypertrophy of

renal tubular epithelial cells. In the middle and late stages, there are gradually increasing mesangial matrix, thickening of glomerular basement membrane, glomerulosclerosis, expansion of some renal tubules, atrophy of some renal tubules, proliferation of interstitial fibrous tissue, etc. The overexpression of TGF B may have different significance in different periods. After the kidney cells are transformed into muscle fibroblasts, the latter will produce excessive extracellular matrix components, and at the same time make the tissues shrink, leading to renal interstitial fibrosis. It is the direct substrate of TGF-B receptor and the intermediary molecule that transmits the signal of ligand receptor interaction from cytoplasm to nucleus. TGF- β the function of signal transduction pathway protein is very complex. Its abnormal expression in the kidney of diabetes rats may be related to the occurrence of DN iron death and chronic progress. The activation of this signal pathway may participate in the process of chronic glomerulosclerosis, leading to renal dysfunction.

Evidence of EMT has been found in interstitial fibrosis model, diabetes model mouse kidney and human kidney, that is, there is smooth muscle actin expression on renal tubules or glomerular epithelial cells, and TGF in positive renal tubular cells- β the expression was significantly increased. It can mediate TGF in mesangial cells- β the effect on fibronectin promoter can mediate TGF in renal interstitial fibroblasts- β Effect on cyclin A activation at TGF- β . It plays an important role in the proliferation and differentiation of cells derived from stroma. In cell culture, TGF- β the increase of the concentration and the secondary activation of the reverse regulatory factor determine its effect. In addition, TGF- β . It can prevent renal tubular epithelial cells and mesangial cells from excessive expiration. However, at this time, the protein synthesis of cells increases, which shows inhibition of proliferation and cell hypertrophy. In addition, excessive apoptosis of renal tubular epithelial cells in the death of DN iron can affect the effective repair of kidney after injury and aggravate renal interstitial fibrosis. Apoptosis and TGF- β . Also related, anti TGF- β Antibody can reduce the degree of apoptosis and renal tubular atrophy.

5. Conclusions

DN has become the third biggest threat to human health in the world. At present, the morbidity and mortality of diabetes in China are rising rapidly. This paper confirms the role of TGF- β in the signaling of iron death in DN. The signaling pathway is involved in the occurrence of glomerulosclerosis and renal interstitial fibrosis in DN by promoting extracellular matrix deposition, epithelial mesenchymal tissue transformation, glomerular and renal tubular cell apoptosis and so on. This provides a new idea for clinical treatment of DN. Pancreatic islet cell injury is closely related to diabetes, and its mechanism may be related to oxidative emergency, endoplasmic reticulum stress, glucose and lipid toxicity, apoptosis and so on. Iron death is an iron-dependent programmed cell death characterized by accumulation of reactive oxygen species in cells. With the deepening of the multi-level research on the influence of TGF- β on renal function, it will undoubtedly make TGF- β become more strategic in grasping the timing and duration of treatment. Excessive therapy can cause excessive cell proliferation, inflammation, autoimmunity and other potentially serious complications. Smad7, as an endogenous TGF- β receptor antagonist, can block the intracellular signal transduction of TGF- β , which provides theoretical basis for gene therapy of DN. In addition, excessive apoptosis of renal tubular epithelial cells in diabetes can affect the effective repair of kidney injury and aggravate renal interstitial fibrosis. Apoptosis is also related to TGF- β . TGF- β antibody can reduce the degree of apoptosis and renal tubular atrophy.

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