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Research Progress on the Mechanism of TXNIP Protein in Diabetic Complications and Related Markers

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Abstract:

TXNIP (Thioredoxin-interacting protein), a key manager of oxidant stress, plays an important role in the pathomechanism of diabetic complications. This review systematically elucidates how TXNIP contributes to diabetic kidney disease (DKD), retinopathy (DR), and peripheral neuropathy through mechanisms involving NLRP3 inflammasome activation and epigenetic modifications. Under high glucose conditions, TXNIP upregulation dissociates from thioredoxin (TRX), binds to NLRP3 via its leucine-rich repeat domain. In DKD, TXNIP overexpression exacerbates renal oxidative stress and mesangial cell apoptosis, while its deficiency preserves β-cell survival and function via AKT/Bcl-xL signaling. In DR, TXNIP inhibition improves angiogenesis and blood-retinal barrier integrity by suppressing NLRP3-mediated inflammation in endothelial cells. Additionally, TXNIP's role in neurodegenerative diseases are linked to glutamate neurotoxicity and NLRP3 activation. Therapeutic strategies include TIX100, a small-molecule inhibitor targeting TXNIP transcription, which effectively ameliorates diabetes in animal models, and moderate NO levels, which protect retinal cells by directly inhibiting TXNIP/NLRP3 signaling. Future research is needed to optimize TXNIP-based therapies for diabetes and metabolic diseases, highlighting its potential as a diagnostic marker and therapeutic target.

Keywords:-TXNIP; NLRP3; mechanism; TRX; treatment

I. Introduction

Diabetic complications are still the main factors leading to the physical and mental suffering of diabetic patients, among which oxidant stress and chronic inflammation are the common basis leading to some diseases of various complications. TXNIP(thioredoxin-interacting protein) is an internal inhibitor of TRX

(thioredoxin) and its expression is significantly up-regulated under high glucose conditions, which can drive the progression of complications through a variety of molecular mechanisms. In recent years, some studies have confirmed that TXNIP can be used to treat diseases like diabetic kidney disease, diabetic retinopathy and diseases like Parkinson's disease and Alzheimer's Disease which can cause the nerves to show signs of degeneration.

But meanwhile, the applications of TXNIP in clinical treatment still has some limits. For instance, the mechanism of action of TXNIP is intricate, as it initially requires binding to TRX (thioredoxin) to suppress TRX activity. This complex mechanism may result in varied effects across different cell types and pathological conditions, thereby complicating its clinical application. Moreover, while drugs leveraging the TXNIP mechanism exhibit potential in regulating cell metabolism, apoptosis, and inflammation, prolonged use might induce certain side effects, such as disrupting glucose metabolism and elevating oxidative stress. Additionally, clinical studies on TXNIP remain relatively limited, with a predominant focus on basic research and animal experiments. Consequently, there is insufficient clinical evidence to substantiate the safety and efficacy of TXNIP in treating specific diseases.

This article aims to systematically review that TXNIP is included in the pathological process of diabetic complications like kidney disease, retinopathy and peripheral neuropathy by regulating the activation of TXNIP/NLRP3 inflammasome and epigenetic modification, and summarize the research progress of potential diagnostic markers and therapeutic targets based on TXNIP.

II. Biological characteristics of TXNIP

A. Basic Protein Structure and Function of TRX and TXNIP

The TRX system contains several antioxidant proteins such as TRX1, TRX2, TRX3 and their reductases TRXR and peroxidoreductases. TRX1 is situated in the extracellular, cytoplasm and nucleus;TRX2 is only in mitochondria and TRX3 is only in spermatids. ASK1 (Apoptosis signaling kinase 1), a MAPK (mitogen-activated protein kinase), is responsible for the activation of the p38 MAPK pathway, leading to apoptosis. TRX-1 can inhibit apoptosis by inhibiting ASK1 ------ Reduced TRX1 binds to the N-terminus of ASK1, inhibits the function of ASK1 as a signal transducer, and induces the degradation of ASK1.

TXNIP is also called the TBP2 (thioredoxin related protein 2) or VDUP1 (vitamin D3 up-regulated protein 1). This protein is the only inhibitor protein that interacts with TRX. TXNIP originally reacted as 1, 25-dihydroxyvitamin D3 gene in HL-60 cells, which is more related to its original name, VDUP1 [1]. The main function of TXNIP is to inhibit the biological function [2] of the binding protein. Under the stimulation of fructose, TXNIP can enter the mitochondria, transfer to the cytoplasmic matrix, and affect the physiological level of ROS (reactive oxygen species) entering the cell membrane. TXNIP manages oxidant stress in our body. TXNIP is a main biological activator of the TRX system where its transcription and stage of biological activity play an important role. TXNIP leads to ASK1-mediated apoptosis pathway of signal. Some studies have shown that TXNIP may induce glucocorticoid-related apoptosis signaling through intracellular ROS scavenging to antagonate the anti-apoptosis effect of TRX [3]. TXNIP can enable the NLRP3 inflammatory body through mediating ER stress, and TXNIP can activate the inflammatory signal through NLRP3, thus playing an extremely important role in cell metabolism. Diabetic complications are still the main factors leading to the physical and mental suffering of diabetic patients, among which oxidant stress and chronic inflammation are the common basis leading to some diseases of various complications. TXNIP(thioredoxin-interacting protein) is an internal inhibitor of TRX (thioredoxin) and its expression is significantly up-regulated under high glucose conditions, which can drive the progression of complications through a variety of molecular mechanisms. In recent years, some studies have confirmed that TXNIP can be used to treat diseases like diabetic kidney disease, diabetic retinopathy and diseases like Parkinson's disease and Alzheimer's Disease which can cause the nerves to show signs of degeneration.

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B. Physiological and Cellular Functions of TXNIP

TXNIP (thioredoxin-interacting protein) exhibits a diverse array of physiological functions and serves as a critical regulator in cellular processes. Primarily, it is involved in redox regulation. By binding to thioredoxin (TRX), TXNIP suppresses its activity of redox enzyme , thereby promoting the amassment of intracellular reactive oxygen species (ROS). Additionally, TXNIP plays an indispensable role in cellular metabolism. Alterations in TXNIP expression levels influence glucose uptake and utilization by cells, as well as lipid synthesis and degradation within the body. Furthermore, TXNIP contributes to the induction of apoptosis by modulating ROS levels and mitochondrial function (Figure 1).

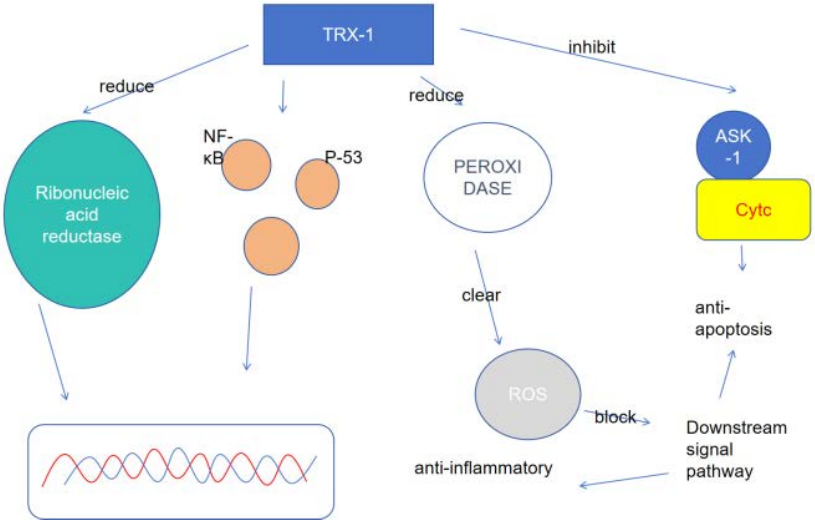

Figure 1. The basic functions of TRX-1.

III. The mechanism of TXNIP in diabetic complications

A. Diabetic Kidney Disease (DKD)

Oxidative stress plays a quite indispensable role in the mechanism of DKD, and one of the main factors is the increase of ROS, which cause DNA damage in cells and eventually leads to cell apoptosis, inducing the generation of ROS, which contributes to the apoptosis of mesangial cells. Overexpression of TXNIP may be mattering the most culprit of oxidative stress in diabetic kidney. When DKD is under oxidative stress, reactive oxygen species promote the separation of TXNIP from TRX and the attachment of TXNIP to NLRP3 via the leucine rich repeat domain. NLRP3 contains three parts: NLRP3 consists of three components: PYD (pyrin domain), LRR (leucine-rich repeat domain) and NACHT (nucleotide-binding oligomerization domain). Being triggered by nuclear factor-κB (NF-κB), which is transported to the nucleus when your body is under oxidative stress conditions.The inflammatory response mediated by PYD, LRR and NACHT is a two-step process. NF-κB command the transcription behavior of NLRP3 and IL-1β and IL-18 in cells. It is confirmed to be the first step in triggering the response of NLRP3 inflammatory. The other step is initiated by TXNIP and NLRP3 through redox-related interactions.

Previous studies have shown that TXNIP is the most severely up-regulated gene [4] in human islet cells exposed to high levels of glucose. Glucose induced a time-dependent and quantitative recruitment of carbohydrate response element-binding protein (ChREBP) to the TXNIP promoter, which regulates TXNIP transcription in human islets.

Moreover, the applications of TXNIP in islet cells from human diabetic patients and diabetic mice may lead to the apoptosis [5.6] of β cells. Exposure to high concentrations of glucose causes the overexpression of TXNIP together with Caspase 3 pathway mediated apoptosis in INS-1 cells and isolated mouse and human islet β cells. This toxicity of glucose which leads to the apoptosis of β-cell was damped in islets from mice deficient in TXNIP [6]. In addition,being short of TXNIP prevents mitochondrial β-cell death through activation of anti-apoptotic AKT/Bcl-xL signaling, and can effectively prevent both type 1 diabetes and type 2 diabetes by regulating the amount of β-cell and its function [6].

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B. DR

Long-term hyperglycemia is the main factor in the development of DR, and glucose transport is a prerequisite for the pathological changes of DR Caused by hyperglycemia. Diabetes mellitus (DM), with increased glucose transport and extracellular glucose accumulation, enhances glucose uptake and metabolism in retinal cells through glycolysis and glycolytic collateral circulation, thereby activating a variety of biochemical pathways ------ including protein kinase C, polyol pathway and renin-angiotensin-aldosterone system. These activated biochemical pathways further increase the output of ROS, which leads to oxidaant stress. When the body is under oxidative stress, reactive oxygen species cause TXNIP to be dissociated from TRX and bound to NLRP3 through the leucine rich repeat domain. The mediated inflammatory response is carried out in two steps ------- Step 1: NF-κB is transported to the nucleus, where it controls the transcription activity of NLRP3 and pro-inflammatory cytokines like IL-1β and IL-18; Step 2: TXNIP and NLRP3 interact with each other in a manner related to redox.

In addition, EC and neurovascular units (NVU) are important components of the blood-retinal barrier (BRB), and experiments have shown that the output level of TXNIP in EC is also remarkably increased. Knocking down TXNIP expression level inhibits the angiogenic response [7], so when TXNIP is inhibited, Therefore, when TXNIP is inhibited, diabetic retinopathy will be improved due to the increase of angiogenesis.

C. NDDs such as AD and PD

The neurotoxicity of glutamate has been shown to be dependent on the activation of TXNIP inflammasome [8]. Treatment related to the culture of hippocampal slice of mice or SH-SY5Y cells with toxic doses could lead to the rise of ROS, ER stress, TXNIP expression and activation of NLRP3 inflammasome [9].

IV. The Applications of TXNIP in the treatment of related diseases

A. TIX100 and DKD

Investigators have been working to identify specific potent oral inhibitors of TXNIP and have used high-output screening of 300,000 small molecules to develop the new chemical entity ------TIX100.Materials and MethodsHigh-fat diet (HFD)-fed mice or severely obese, leptin-deficient ob/ob mice were randomly assigned to serve as controls or receive oral TIX100, a novel thioredoxin-interacting protein (TXNIP) inhibitor just approved by the FDA as an investigational new drug for type 1 diabetes (T1D). The TIX100 effects on glucose intolerance and weight control were then under assessment. Results are that TIX100 could protect body from HFD-induced glucose intolerance, high level of insulin and high level of sugar in blood. TIX100 also lessened diet-related obesity resulting in a 15% lower of weight in mice under treatment when being compared with controls on HFD, while preserving the amount of muscle. The improvement of glucose control caused by TIX100 leads to a 2.3% reduction in the output of HbA1C, though the effects of TIX100 on weight were found lost from time to time. This is in line with the positive influence of TIX100 in diabetes models with normal weight and its conservation against enhanced TXNIP and stress of islet cell and its almost common to all diabetes types [10].

Consequently, TIX100 provides a fresh, oral medication for type 2 diabetes that targets at potential diseases pathology including islet cells disorder and high concentration of the level of blood sugar and promotes the health of metabolic process and weight control without aggressive weight loss . In line with previous studies, TIX100 was exactly effective in down-regulating the expression of TXNIP in rodent and human islet cells and rescued type 2 and type 1 diabetic mouse models. What is more, TIX100 was found to significantly reduce serum glucagon level without affecting the effect of glucagon on hypoglycemia, thus effectively preventing hypoglycemia (Figure 2).

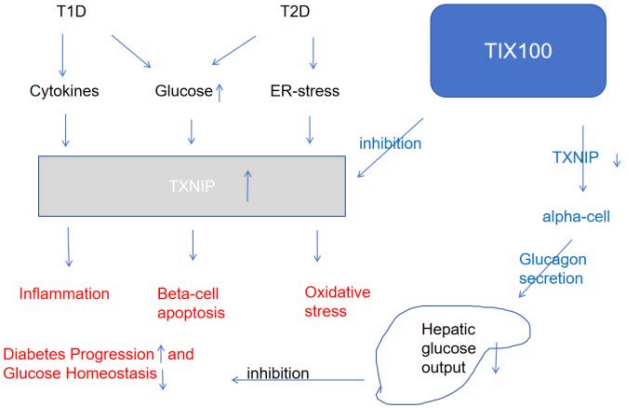

Figure 2. The relationship between diabetes and TXNIP and the mechanism of action of the chemical entity TIX100.

Mechanistically, TIX100 functions at the molecular level by inhibiting TXNIP transcription through a specific 20 bp region containing an E-box in the TXNIP promoter as demonstrated by TXNIP promoter analyses, luciferase assays and chromatin immunoprecipitation studies.

Meanwhile, TIX100 is a small salt formulation, so it is

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water soluble and can easily be take orally.

B. NO versus DR

Hyperglycemia promotes the sensitization of TXNIP inflammasome signaling and up-regulates the output of IL-1β and inducible NO synthase (iNOS), thereby increasing the release of NO. Moderate levels of NO have a protective effect on retinal endothelial cells and neurovascular unit (NVU) by directly inhibiting TXNIP/NLRP3 inflammasomes or inhibiting NLRP3 inflammasomes assembly and TXNIP/NLRP3 inflammasomes signal transduction, thus having a certain therapeutic effect on diabetic retinopathy (Figure 3).

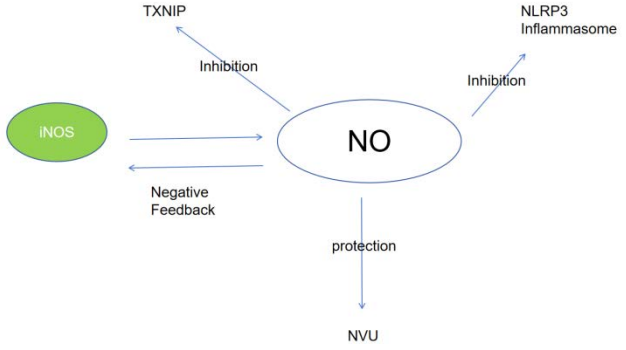

Figure 3. Relevant mechanisms of action of NO.

V. Conclusions

Taken together, TXNIP interacts with TRX to adjust the level of ROS, thereby modulating the oxidant stress status in the body. Additionally, TXNIP can activate the NLRP3 inflammasome, which plays an indispensable role in the management of apoptosis. This thesis elucidates the potential mechanisms of TXNIP in diabetic kidney disease (DKD), diabetic retinopathy (DR), and other NDDs, while proposing potential therapeutic strategies based on these mechanisms.

Taking the application of TXNIP in DKD treatment as an example, the chemical entity TIX100 has demonstrated initial success in mouse experiments. However, its clinical application remains limited due to potential side effects that require further investigation. Therefore, more comprehensive development of TXNIP inhibitors with reduced side effects is warranted.

This paper provides an outline of the mechanisms and utilization of TXNIP but lacks integration with clinical data, which may introduce limitations in the robustness of conclusions and the reliability of inferences. Furthermore, no comparative analysis has been conducted regarding the efficacy, safety, and cost-effectiveness of TXNIP-based treatments relative to other therapeutic approaches for related diseases.

Future studies should focus on evaluating the reliability and short- and long-term side effects of TXNIP-related agents or chemical entities. Simultan`eously, efforts should be directed toward developing drugs with faster onset of action and fewer adverse effects.

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