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Thioredoxin-Interacting Protein: The Redoxissome Complex in Glomerular Lesion

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ABSTRACT

Chronic Kidney Disease (CKD) affects millions of people worldwide and is a global health problem with few treatment options. The mechanisms underlying the pathogenesis of CKD include oxidative damage and inflammation. Damage to the glomeruli may be observed during the course of co-associated diseases such diabetes, but also in specific conditions such as focal segmental glomerulosclerosis. During its early manifestation, podocyte's damage and death are key factors to glomerulopathies and its protection may represent an important therapeutic approach. Importantly, podocytes pathology involves inflammation and cellular damage, principally due to excessive oxidative stress. Underlying mechanisms associated to both inflammation and oxidative stress during the course of a renal lesion must be elucidated for the development of better clinical and research approaches to kidney physiology. Thus, here we discuss the role of the Thioredoxin system, an antioxidant mechanism, and TXNIP, a thioredoxin inhibitor linked to NRLP3 inflammasome activation, as a pivotal axis in the pathophysiology of glomerular lesions.

Keywords: Oxidative stress, Inflammasome, Thioredoxin, TXNIP, Podocytes, Focal Segmental Glomerulosclerosis

GLOMERULAR LESIONS, OXIDATIVE STRESS, REDOX SYSTEM AND INFLAMMATORY MECHANISMS OF RENAL DAMAGE

Chronic kidney disease (CKD) is estimated to affect roughly 13.4% of the world's population (1). Damage to renal tissue can occur from different underlying conditions and mechanisms, including infections, hemodynamic changes, and direct injury to renal components. Glomeruli damage currently accounts for 25% of the total kidney lesions observed in the adult population, with a higher incidence among the young population (2).

Focal Segmentar Glomerulosclerosis (FSGS) is a histologic pattern of lesion of the glomeruli characterized by the focal manifestation of sclerotic lesions in some glomeruli, and segmental fibrosis observed in portions

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of the affect glomeruli. It is believed that FSGS manifestation begin with damage to podocytes, a highly specialized cell that composes the glomerular filtration barrier, causing its death and detachment from the glomerular basal membrane. This process exposes the basal membrane and scar formation initiates from the contact of the basal membrane and parietal epithelial cells (3).

The manifestation of FSGS is highly correlated with the expression of inflammation markers. The analysis of gene expression profile of FSGS patients after renal transplant, revealed a differential expression of genes primarily involved with inflammation process, such as nuclear factor-κB (NF-κB) and cytokines (IL-1β), which could be related with the organ reperfusion process considering the contact of the allograft with the serum of the patient (4).

Besides the role of inflammation in the pathogenesis of FSGS and glomerular damage, oxidative stress has also been observed as a major factor present in the initial manifestation of glomerular damage.

One mechanism of podocyte injury can occur after cellular stimuli and crosstalk between podocyte and glomerular endothelial cells. The paracrine communication mediated by molecules secreted by podocytes such as Endothelin-1, induces mitochondrial stress causing dysfunction of endothelial glomerular cells, leading to later mechanisms of podocyte apoptosis (5). Hence, the understanding of the cellular oxidation process can be a strategy for alternative treatments in FSGS.

Faced with oxidative insult, the cell normally activates its redox system wherethe "thioredoxin axis" is a powerful reductor agent acting in the oxidated protein, decreasing the cellular stress signaling and activation. Here we discuss the role of the Thioredoxin system, an antioxidant mechanism, and TXNIP, an endogenous thioredoxin inhibitor, as a pivotal axis in the pathophysiology of glomerular lesion.

THIOREDOXIN

Thioredoxin (Trx) proteins are part of a key antioxidant system highly preserved in many organisms, ranging from archaea to mammals (6). Trx was firstly described as an electron donor for ribonucleotide reductase, with subsequent roles discovered as in redox control, growth factor and inflammatory response activity (6). In mammals, two isoforms of Trx are present and distinguish between its location. Thioredoxin-1 (Trx1) is located mainly in the cytosol, but is also present in the nuclei, plasma membrane and has extracellular activity, while Thioredoxin-2 (Trx2) is located in the mitochondria (7,8).

Trx is induced by metabolic components such as estrogen, prostaglandins and cAMP, and different stimuli, such as virus infection, ischemia reperfusion and hydrogen peroxide (7). Nuclear factor erythroid 2 like 2 (NRF2) is a master antioxidant pathway activated upon reactive oxygen species (ROS) production that promotes the upregulation of over 250 genes involved in processes of redox homeostasis, carbohydrate and lipid metabolism, DNA repair and more, including Trx (9).

Trx reductase activity is performed by reaction with thiol-oxidized proteins where Trx constantly alternates between reduced and oxidized forms and is reduced back by thioredoxin reductase, an enzyme that catalyzes the electron transport from the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) to the oxidized Trx (6,8). Furthermore, Trx1 is capable of binding and modulation of proteins such as NfκB, p53, glucocorticoid receptor, estrogen receptor and others by its thiol-disulfide reaction, with a reported anti-inflammatory response in both intra and extracellular environments (7) and it seems to be involved in responses of cellular growth and cell death, with increased levels in tumoral cells (10).

Thioredoxin Interaction Protein and Redoxissome Complex Signaling

Firstly described as Thioredoxin Binding Protein 2 (TBP-2), a molecule identical to a protein previously named Vitamin D-upregulated protein 1 (VDUP-1), the Thioredoxin interaction protein (TXNIP) is an oxidant, apoptotic molecule and endogenous Trx inhibitor (11) that binds to the reduced form of both Trx isoforms, in a disulfide exchange reaction with the reduced Trx that is unique to the TXNIP (7). When translocated to the mitochondria, TXNIP interaction with Trx2 causes mitochondrial dysfunction, since Trx2 inhibits apoptosis signal regulation kinase 1 (Ask1), while TXNIP translocation also results in increased reactive oxygen species (ROS) accumulation and increases NLRP3 inflammasome activation in the mitochondria (7). In response to endoplasmic reticulum stress, TXNIP favors the paths of programmed cell death due to unbalance and accumulation of the unfolded protein response (8). While Trx is upregulated in many human tumors, TXNIP acts as a tumor suppressor and is downregulated in many cancers (10). This relation illustrates the complex mechanisms of Trx/TXNIP interaction in homeostasis and diseases status, since the regulation of Trx components may protect against oxidative damage and inflammation in several pathologies while the opposite could be observed in the tumoral tissue.

Thus, considering the involvement of Trx/Txnip axis during mechanisms related to cellular environment and diseases, Yoshihara *et al.* suggested that this signaling complex composed by Trx and Txnip should therefore be called "Redoxis some" (7).

TXNIP as an Inflammation Component

Currently, TXNIP response in different mechanisms vary from oxidative stress and inflammation. One function attributed to TXNIP is the activation of NOD-like receptor protein-3 (NLRP3) inflammasome in a redox dependent manner. This multi-protein complex, composed of NLRP3 oligomers, caspase-1, apoptosis-associated speck-like protein containing caspase recruitment domain (ASC), regulates the innate immune response causing the activation of caspase-1 and further activation of interleukin(IL)-1β. These complexes detect and trigger respons-

es over stimuli as cellular damage and stress, where TXNIP is suggested as playing the communication from the redox disturbance present in the latter to the activation of inflammasome (8,10)

Upon oxidative stress, the increase in ROS causes the oxidation of the disulfide bond between TXNIP and the reduced Trx, leading to the dissociation of the TXNIP/Trx complex (10). As a consequence and response to ROS, Trx may act in its antioxidant pathway, and TXNIP is now available to turn in its inflammatory responses, such as directly interacting with NLRP3 inflammasome (8).

Interestingly, Yoshihara *et al.* highlight conflicting reports over NLRP3 activation by TXNIP (7). While some suggest an increase in TXNIP-NRLP3 interaction under oxidative stress, the authors suggest the existence of another component involved in the Trx response that is also necessary in the NLRP3 response to oxidative stress, emphasizing the existence of a redoxissome complex composed by molecules that participate in the Trx reducing process.

While still in debate, early studies had suggested that TXNIP is the mediator of the NLRP3 inflammasome activation. This is supported by results showing that the products of NRLP3, activation of caspase-1 and secretion of mature IL-1 β were less present when ablation of TXNIP was promoted together with use of the inflammasome activators (12). This interaction of TXNIP and the activation of NLRP3 response is implicated to be present in different diseases such as obesity-induced insulin resistance, metabolic disorders in ischemic heart and type 1 and type 2 diabetes (8).

Interestingly, TXNIP also activates NF-κB. NF-κB is a transcriptional factor involved in the inflammatory response that leads to the expression of pro-inflammatory genes. Human macrophages (U937) transfected with a siRNA for TXNIP expressed reduced levels of both: i) phosphorylated nuclear factor inhibitor alpha (pIκBα), crucial component of Nf-κB activation, and ii) phosphorylated-NF-κB after inflammatory stimuli, as well as attenuated cytokines and inflammatory molecules (13).

The Glomerular Lesion and TXNIP

TXNIP has been associated with processes of inflammation, fibrosis and ROS lesion in diabetic nephropathy (14) along with damage and apoptosis in podocytes (15). TXNIP is induced by hyperglycemia, thus its role in the development of diabetic nephropathy is remarkable for its impairment of thioredoxin activity in a glucosis-induced manner.

Markers of renal injury present in diabetic nephropathy such as albuminuria, proteinuria and serum creatinine were not increased in response to TXNIP knockout in a streptozotocin diabetic mice model, along with lesser histological manifestation of renal lesions due to the absence of TXNIP (16). The inhibition of TXNIP gene expression results in reduced renal interstitial collagen deposition induced by diabetes and reduced type I collagen of interstitial areas of diabetic rat kidneys (17). Furthermore, TXNIP silencing in podocytes reduced apoptosis via interaction with the mTOR pathway and could reduce renal damage by modulation of p38 MAPK phosphorolation (15). Additionally, TXNIP knockout mitigated podocyte foot process effacement and contributed to the maintenance of glomerular barrier membrane thickness in the diabetic nephropathy model (16).

Moreover, the role of TXNIP in glomerular injury was verified by the direct interaction found between TXNIP and NRLP3 inflammasome activation in cultured human podocytes (18). In response to advanced-glycation end products, compounds resulting from the process of ageing as well as inflammation and hyperglycemia, TXNIP was highly expressed in glomerulus and podocyte, where the epigenetic machinery of pos-translational histone modifications are reported to be regulators of TXNIP expression under hyperglycemia and advanced-glycation products exposure (19). In the context of FSGS patients, increased TXNIP level was detected in urinary sediments when compared to healthy individuals, while the same occur in diabetic nephropathy patients (20). Further involvement of TXNIP in cellular components of renal physiology are shown in Table 1.

These evidences suggest that TXNIP is an important factor in inflammatory and oxidative response for its capability of reducing Trx activity and promoting key inflammatory agents such as NRLP3 inflammasome and NF-κB activation. Consequently, further interventions that result in a regulatory response decreasing TXNIP levels, resulting in increased Trx activity could lead to interesting therapeutic approaches.

For its activity in several physiological responses, systemic inhibition of TXNIP could be useful beyond promoting moderate risk including dysregulation of its proapoptotic activity. In this sense, the use of antioxidants, including natural pharmacological active compounds, have been shown to modulate TXNIP and NLRP3 inflammasome together with its antioxidant activity. In this manner, modulation of TXNIP expression may result in interesting pharmacological responses. Known mechanisms of TXNIP synthesis promotion includes vitamin D_3, hence the previous name of the identical described protein vitamin D-upregulated protein-1 (VDUP-1), heat shock protein and PPAR α and γ. Although many different molecules interact with the TXNIP gene promoter region, one of the main stimuli for its synthesis is the raise in glucose concentration (21).

On the other hand, inhibitory effects on TXNIP expression and augment of TXNIP clearance are promoted by pharmacological hypoglycemic compounds. Administration of insulin or Metformin suppresses TXNIP expression while also accelerating TXNIP degradation in different tissues (21). While this suggests asignificant role of TXNIP in diabetes and its associated pathologies, interaction between TXNIP and pathological mechanisms independent of glucose disturbances or compounds not related to glucose metabolism found in different studies highlights the many capabilities of TXNIP.

As discussed by Mohamed *et al.* (2021), the use of traditional medicine compounds such as Taohong Siwu decoction, Z-Gug-

Table 1. Kidney cellular components responses over TXNIP modulation.

Cell	Mechanism	Effect on TXNIP	Cellular response	Reference
Podocyte	Inhibition of S-adenosylhomocysteine hydrolase promotes inhibition of EZH2 and reduction in H3K27me3 and upregulates TXNIP.	↑	↑ NLRP3 activation ↑ ROS ↑ Podocyte cell death	(26), (27)
	Activators of AMPK suppress TXNIP expression levels.	↓	↑ AMPK ↑ Thioredoxin reductase activity	(28)
	gp91^{phox} overexpression is induced by TXNIP in high-glucose exposed podocytes; inhibition of TXNIP reduced F-actin fibers loss from high-glucose exposure in podocytes.	↓	↓ gp91^{phox} ↑ F-actin fibers, otherwise reduced during the lesion model	(29)
	Silencing of TXNIP in high-glucose induced podocytes reduced NLRP3, caspase-1 and IL-1β production/activity.	↓	↓ NLRP3 activation ↓ caspase-1 activity ↓ IL-1β production ↑ F-actin fibers, otherwise reduced during the lesion model	(18)
	Knockdown of TXNIP in murine podocyte suppresses the activation of mTORC1 and mTORC2, downregulates Nox1 and Nox4 expression and prevents p38 MAPK phosphorylation.	↓	↓ Epithelial-to-mesenchymal transition ↓ ROS ↓ Podocyte cell death	(30), (15)
	H_2S promote binding disruption of Trx from TXNIP in mouse podocyte.	-	↑ Trx availability; prevention of oxidative podocyte injury	(31)
Glomerular mesangial cells	Inhibition of S-adenosylhomocysteine hydrolase promotes inhibition of EZH2 upregulates TXNIP in rat mesangial cell.	↑	↑ TXNIP mRNA levels	(27)
	Exposure to high glucose and LPS increased expression of mRNA and protein of TXNIP and NLRP3 inflammasome.	↑	↑ NLRP3 ↑ procaspase-1 ↑ IL-1β	(32)
	Silencing of TXNIP inhibits expression of NLRP3, ASC and caspase-1.	↓	↓ Cell proliferation ↑ SOD activity ↓ Collagen IV	(33)
	Silencing of TXNIP suppressed high-glucose induced ASK1 phosphorylation and cleaved caspase-3 expression in mouse mesangial cells.	↓	↓ ASK1 phosphorylation ↓ cleaved caspase-3	(34)
	Absence of TXNIP protein inhibited Collagen IV deposition and ROS after 24h-treatment in high-glucose exposure of mouse mesangial cells.	↓	↓ Collagen IV ↓ ROS	(35)
	Silencing of TXNIP and activation of AMPK further inhibited TXNIP mRNA expression levels.	↓	↓ ROS ↑ SOD activity ↑ CAT activity ↑ Cell viability	(36)
Tubular renal cells	Inhibition of S-adenosylhomocysteine hydrolase promotes inhibition of EZH2 upregulates TXNIP in NRK-52E and MDCK cells.	↑	↑ TXNIP mRNA levels	(27)
	IL-1β induces expression of TXNIP and Nox4 in HK-2 tubular cells.	↑	↑ ROS	(37)

Table 1. Kidney cellular components responses over TXNIP modulation. **(continued)**

Cell	Mechanism	Effect on TXNIP	Cellular response	Reference
	TRPV4 agonists increases TXNIP level in NRK-52E cells through increase of intracellular Ca^{2+}.	↑	↑ Cell injury	(38)
	Knockdown of TXNIP on NRK-E52 tubular cells protected the cells over ADR administration.	↓	↑ Cellular viability ↑ p-P38	(28)
	Silencing of TXNIP reduces mitophagy regulator protein BNIP3 and suppress phosphorylation of mTOR by high glucose.	↓	↓ ATP production impairment ↓ mitochondrial ROS ↓ mitophagy	(17)

Differential responses of kidney cellular components to modulations of TXNIP and its effects. ADR: Adriamycin. AMPK: 5'-AMP-activated protein kinase. ASK1: Apoptosis signal-regulating kinase 1. CAT: Catalase. EZH2: enhancer of zeste homolog 2. FN: Fibronectin. H_2S: Hydrogen sulphide. H3K27me3: trimethylation of histone 3 lysine 27. IL: interleukin. LPS: lipopolysaccharide. MAPK: p38 mitogen-activated protein kinase. mTOR: mammalian target of rapamycin complex. NLRP3: nod-like receptor protein 3. p-P38: phosphorylated P-38. ROS: Reactive oxygen species. SOD: superoxide dismutase. Trx: Thioredoxin. TXNIP: Thioredoxin-interacting protein

gulsterone, an herbal steroid, Umbelliferone, natural antioxidant, Curcumin, antioxidant extracted from *Curcuma longa*, and other pharmacological therapies as Verapamil and Metformin; all together can promote modulation of TXNIP activity and TXNIP-NRLP3 inflammasome activation in severe disease models. Some of the reported effects include attenuation of ischemic brain injury, prevention of fatty liver, improvement of hyperglycemic stroke damage, and several diabetes-related complications via TXNIP and TXNIP-NLRP3 inflammasome activation (22).

For instance, use of curcumin in a model of ischemic reperfusion leads to a decrease in Nf-κB expression, while also reducing TXNIP protein and mRNA levels present in tubules during the renal ischemic reperfusion injury, promoting cytoprotective effects against oxidative stress (23). Furthermore, curcumin also presents modulation of TXNIP in neurotoxicity (24) and promotion of Trx1 during prostate cancer (25). Not only acting as a regulator of TXNIP, curcumin also has an important antioxidant activity by activation of Nuclear factor erythroid 2-related factor 2 (NRF2), promoting the expression of many others antioxidants enzymes, such as Heme Oxygenase-1 and superoxide dismutase (24), indicating that modulation of TXNIP is included in its functional activity. A brief overview and mechanisms of TXNIP activity over inflammation and oxidative stress are summarised in Figure 1.

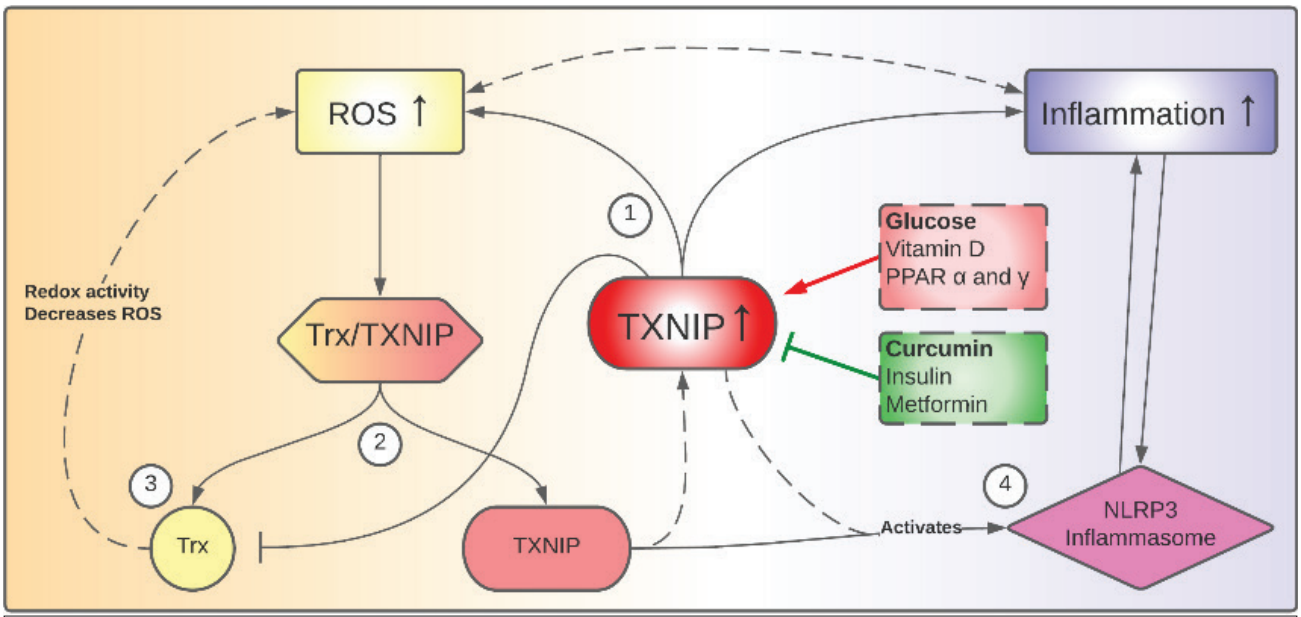

Figure 1. TXNIP acting as a link between inflammation and oxidative stress. (1) Increased TXNIP leads to ROS by inhibition of Trx redox activity. (2) Increased ROS causes dissociation of Trx/TXNIP complex. This dissociation frees (3) Trx to its antioxidant response and (4) TXNIP to act as an activator of NLRP3 in a ROS-dependent response.

CONCLUSION

In summary, Trx and TXNIP are involved in the mechanisms of homeostasis and progression of a variety of diseases, ranging from cancer to diabetes and kidney disease, and are highly expressed in damage tissues by inflammation and/or oxidative stress. Being involved in both mechanisms of glomerular lesions, TXNIP is a molecule of high importance in the pathogenesis of several diseases and may represent a key factor and a link for the oxidative response and inflammatory mechanisms. While overexpressed, TXNIP may contribute to the progression of different pathologies, however, its downregulation can contribute to cancer growth and migration, due to its role in cell apoptosis, while also improving the redox mechanism. Therefore, the elucidation of TXNIP axis role in diseases such as its modulation in FSGS could contribute to the understanding of the global pathophysiology of most chronic kidney diseases, as well as others related to renal disfunctions.

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