# Thioredoxin-Interacting Protein

Subjects: Immunology

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The development of new therapeutic approaches to diseases relies on the identification of key molecular targets involved in amplifying disease processes. One such molecule is thioredoxin-interacting protein (TXNIP), also designated thioredoxin-binding protein-2 (TBP-2), a member of the α-arrestin family of proteins and a central regulator of glucose and lipid metabolism, involved in diabetes-associated vascular endothelial dysfunction and inflammation. TXNIP sequesters reduced thioredoxin (TRX), inhibiting its function, resulting in increased oxidative stress. Many different cellular stress factors regulate TXNIP expression, including high glucose, endoplasmic reticulum stress, free radicals, hypoxia, nitric oxide, insulin, and adenosine-containing molecules. TXNIP is also directly involved in inflammatory activation through its interaction with the nucleotide-binding domain, leucine-rich-containing family, and pyrin domain-containing-3 (NLRP3) inflammasome complex. Neurodegenerative diseases such as Alzheimer's disease have significant pathologies associated with increased oxidative stress, inflammation, and vascular dysfunctions.

Keywords: oxidative stress ; inflammation ; Alzheimer's disease ; glucose metabolism ; neuropathology

## 1. Introduction

Oxidative stress resulting from an imbalance in cellular redox can occur due to the production of excessive levels of reactive oxygen species (ROS) and/or a deficit of cellular antioxidant systems. Supplementation with various classes of antioxidants has been widely investigated for neurodegenerative diseases (for recent reviews, see [1][2]). Excess levels of ROS can occur from inflammatory responses by innate immune cells (e.g., neutrophils, monocytes/macrophages/microglia) due to infections or chronic autoimmune responses [2], deficiencies in mitochondrial oxidative phosphorylation pathways [3][4], and environmental factors such as UV light, toxic chemicals, or heavy metals. Oxidative stress is linked to many different chronic human diseases, particularly those with inflammatory and/or metabolic components (e.g., diabetes and diabetes-related retinopathy [5], stroke [6], cancers [7], vascular diseases, and neurodegenerative diseases [8][9]). Developing effective therapies for these diseases requires the identification of key pathological targets responsible for amplifying disease processes.

Thioredoxin-interacting protein (TXNIP) has emerged as a key pathological regulator of diseases, particularly those associated with glucose and lipid abnormalities and inflammation. TXNIP has been identified in disease mechanisms involved in various cancers [10][11][12], diabetes mellitus [13], cardiovascular disease [14], renal disease [15], and retinal disease [16], among others. Many of these diseases associated with TXNIP can arise from vascular complications of diabetes [17]. The involvement of TXNIP in diabetes, pancreatic beta-cell death, and glucose metabolism has been the focus of several recent review articles [14][17][18]. TXNIP was identified (and named) due to its interaction and inhibition of the key antioxidant proteins thioredoxin-1 (TRX1) and thioredoxin-2 (TRX2) [19][20][21], but more recent findings identified properties involved in cellular metabolism and transcription regulation [22], apoptosis and cell death [13], inflammation [23], and tumor suppression [11][24] that might not be directly related to the modulation of TRX and oxidative stress.

## 2. Biochemistry of TXNIP: Overview

The gene for TXNIP is located on the human chromosome 1q21.1 and is transcribed to four messenger RNA (mRNA) splice variants [25]. TXNIP is a member of the α-arrestin protein family and has two arrestin-like domains: one is a PxxP sequence and the other is a PPxY sequence. One mRNA for TXNIP codes for 336 amino acids for a polypeptide of approximately 37.4 kDa, whereas another codes for 391 amino acids for a polypeptide of approximately 43.7 kDa. The two other splice variants have not been associated with proteins. Reported molecular weights of TXNIP vary depending on the expressing cell type, but the major protein band(s) detected by SDS-gel electrophoresis is/are 50–55 kDa. This would suggest a certain amount of post-translational modification occurring. Protein bands of approximately 37 kDa have been observed on immunoblots with certain antibodies and cell types, but 50–55 kDa polypeptides appear to be the major form. TXNIP was identified initially by several investigators as vitamin D3-upregulated protein-1 (VDUP1) in different cell

types [19][20][21]. Interestingly, other studies have not confirmed TXNIP induction by vitamin D3 in additional cell types, and noticeably, there is a lack of a vitamin D3-responsive element in the TXNIP gene promoter [26][27]. It has been suggested that vitamin D3 stabilizes cellular TXNIP protein rather than inducing expression [26].

### 2.1. TXNIP and Thioredoxin System

Earlier studies provided the first link between VDUP1/TXNIP and oxidative stress by demonstrating binding to reduced, but not oxidized, thioredoxin (TRX) [19][20][21]. TXNIP can bind two cysteine residues (Cys32 and Cys35) present in the active catalytic site of TRX. The binding of oxidized TXNIP to reduced TRX involves the formation of disulfide bonds between TXNIP-Cys247 and TRX-Cys32 [28]. A mutation in TXNIP-Cys247 is sufficient to remove its ability to sequester TRX activity [28]. Although classified as belonging to the α-arrestin family, these cysteine residues are unique to TXNIP. TXNIP can bind and inactivate both TRX1 and TRX2 [19][29]. The TRX cellular disulfide oxidoreductase system is a highly conserved system found from prokaryotes to plants to mammals [30][31][32]. TRX plays a central role in protecting cells from oxidative stress. Oxidized TRX is reduced by NADPH through a reaction catalyzed by thioredoxin reductase complex (TRX-R). Reduced TRX can then directly reduce disulfides in target proteins [30]. The main form of TRX is TRX1, which is located primarily in the cytosol but can be translocated to the plasma membrane and/or nucleus, particularly under inflammatory conditions [33][34]. Closely related in structure, TRX2 is specific to mitochondria [35][36]. Immunohistochemistry and in situ hybridization mRNA studies have shown that TRX was highly expressed in mammalian brains, particularly in subsets of neurons in areas of high metabolic activity and oxidative burden [37][38][39]. TRX mRNA expression was highest in the piliform cortex, dentate gyrus, CA3/CA4 region of the hippocampus, locus coeruleus, and nucleus of the hypothalamus and solitary tract [38]. Trx2 mRNA and protein were highly expressed in rat brains in neurons in the olfactory bulb, frontal cortex, hippocampus, some hypothalamic and thalamic nuclei, cerebellum, and numerous brainstem nuclei [39].

The significance of the TRX system for maintaining cellular health was demonstrated in transgenic mice overexpressing forms of TRX. Increased expression of human TRX in mice resulted in resistance to oxidative stress and increased lifespan [40]. Other studies have shown that TRX overexpression in transgenic mice was protective of transient ischemic brain damage [41]. This effect was also observed by intravenous administration of TRX protein [42]. These examples of the beneficial outcomes of increased TRX are used to introduce the widely appreciated pathological consequences of reduced TRX activity. The first study linking TRX to AD showed a significant reduction in TRX protein levels in most brain regions in AD cases compared to nondemented controls with accompanying increased TRX-R activity. This study also demonstrated the protective effect of TRX when added to cultures of neurons treated with toxic doses of amyloid beta (Aβ) peptide [43]. A further study showed that TRX1 levels were increased significantly in the cerebrospinal fluid (CSF) and plasma of AD cases compared to mild cognitive impairment (MCI) cases [44]. This suggested that TRX1 was being secreted from damaged neurons in AD brains. A noticeable alteration in the patterns of TRX1 and TRX2 cellular immunoreactivity in hippocampal neurons of AD cases was also observed.

### 2.2. TXNIP Interacting Proteins

TXNIP has been shown to interact with other proteins besides TRX, including importin-α1 [45], human ecdysoneless (hEcd) [46], and NOD-, LRR-, and pyrin domain-containing protein-3 (NLRP3), a component of the inflammasome complex [23][47]. These interactions relate to additional identified properties of TXNIP. The significance of the interaction of TXNIP with inflammasome components and enhancement of inflammation will be considered.

## 3. Regulation of TXNIP Expression

Many different cellular stress factors positively or negatively regulate TXNIP expression. These include UV light, heat shock [48], hypoxia, ROS, nitric oxide [49], nicotinamide adenine dinucleotide [50], ATP, glutamine, nicotine, vascular endothelial growth factor, basic fibroblast growth factor [51], transforming growth factor β [52], estradiol [53], calcium channel blockers [54], activators of advanced glycation endoproduct receptor (RAGE) [55], insulin, and glucose [56]. Activation of the TXNIP promoter, which contains a carbohydrate response element (ChoRE), is regulated by transcription factors MondoA:Max-like protein X (MLx), nuclear factor Y (NF-Y), and the carbohydrate response element-binding protein (ChREBP) [42]. Transcription factors forkhead box O1 (FOXO1) and FOXO3a can bind to the TXNIP promoter and by competing with ChREBP can downregulate TXNIP transcription [43][44]. Activation of AMP protein kinase (AMPK) can also lead to inhibition of TXNIP mRNA transcription [45].

The mechanism whereby TXNIP expression is induced through the activation of the receptor for advanced glycation endproducts (RAGE) by the RAGE ligand S100b is of relevance for th consideration of AD as RAGE is a receptor for Aβ and is involved in Aβ toxicity and AD pathogenesis [55]. It was demonstrated in Schwann cells in vitro and injured sciatic

nerve in vivo that binding of S100b to RAGE induced TXNIP with TXNIP being involved in the downstream activation of p38 mitogen-activated protein kinase (MAPK), cAMP response element-binding protein (CREB), and nuclear factor κB (NFκB). RAGE silencing blocked the induction of TXNIP, whereas the silencing of TXNIP inhibited the activation of these signaling pathways, preventing RAGE-induced fibronectin and IL1β synthesis and Schwann cell migration [55]. Induction of TXNIP by RAGE ligands in retinal endothelial cells through the activation of p38 MAPK and NFκB also led to enhanced expression of inflammation-associated genes, including cyclooxygenase 2 (*Cox2*), vascular endothelial growth factor (*VEGFA*), and intercellular adhesion molecule-1 (*ICAM1*). Expression of these genes was reduced when TXNIP expression was inhibited, and enhanced with TXNIP overexpression [57].

## 4. TXNIP, Hyperglycemia, and Oxidative Stress—NLRP3 Inflammasome Complex

Presentations of research data on TXNIP in relation to disease have frequently considered TXNIP/TRX interactions and the resulting oxidative stress as a separate mechanism from its role in the NLRP3 inflammasome activation, but these two features are interrelated. Although associated with enhanced inflammation, NLRP3 inflammasome activation occurs in all brain cell types, including neurons, astrocytes, and endothelial cells, not just microglia [58][59]. If one considers the events occurring under hyperglycemic conditions, excess glucose leads to increased levels of ROS by inducing the overproduction of NADH and increased mitochondrial-derived ROS that inhibits GAPDH, the enzyme that removes excess cellular glucose [60]. However, this inhibition that activates alternative glucose metabolic pathways leads to further ROS production. Excess ROS directly induces the expression of TXNIP and the inflammation-associated transcription factor NFκB. Excess TXNIP will further exacerbate oxidative stress by binding TRX and, in cooperation with NFκB, bind and activate the inflammasome complex. The inflammasome complex consists of an association of NLRP3, apoptosis-associated speck-like protein containing a caspase-binding domain (ASC) and pro-caspase-1 [61][62]. In the presence of excess ROS, TXNIP interaction with TRX can be reversed, which then allows released TXNIP to bind and activate NLRP3 inflammasome, resulting in enhanced inflammation. Activation of NLRP3-inflammasome promotes the formation of activated caspase-1, which processes interleukin (IL)-1β, IL-18, and IL-33 into bioactive forms [63], and also induces cell death through pyroptosis [64]. An earlier study also demonstrated that inflammasome activators such as uric acid crystals induced the dissociation of TXNIP from TRX in the presence of ROS, allowing it to bind and activate the NLRP3 complex and enhance caspase activation [47].

## 5. TXNIP Expression in the Brain

Studies focusing on the cellular distribution of TXNIP in brain cells are limited. Detailed immunochemical characterization of TXNIP/VDUP1 by comparing its distribution in *Drosophila* and rat brains showed relatively conserved patterns of expression. The antibodies employed in this study identified this protein in both of these species. Constitutive expression in subsets of neurons and astrocytes were identified using double immunohistochemistry staining with appropriate markers. This study did not report the constitutive microglial expression of TXNIP but observed nuclear immunoreactivity under hyperglycemic conditions [65]. A further study employed immunohistochemistry to compare the neuroanatomical distribution of different TRXs, TRRs, glutathione/glutaredoxin, peroxiredoxins, and TXNIP in rat brains. Expression of these antioxidants and related molecules was highest in brain regions susceptible to damage in conditions of hypoxia/ischemia including the cerebellum, cortex, hippocampus, substantia nigra, striatum, and spinal cord. Weak expression of TXNIP was detected in subsets of neurons, not glia, in these brain regions, except the spinal cord, and with the highest expression in the retina. The pattern of expression of TRX1 and TXNIP showed extensive overlap [66]. A direct link between metabolic activity and TXNIP was demonstrated in mice with the expression of TXNIP in medial hypothalamic neurons, which increased under conditions of nutrient excess and obesity [67]. A further study using directed TXNIP gene deletion and overexpression in *Agrp* hypothalamic neurons showed that the overexpression of TXNIP led to reduced energy expenditure and activity, resulting in obesity and fat accumulations, whereas the deletion of TXNIP in *Agrp* neurons had a reverse effect, with increased energy metabolism and activity [68]. Another study showed strong induction of TXNIP in the hypothalamus of mice in a state of lowered energy metabolism, though increased TXNIP expression was detected in ependymal-lining cells, not neurons, in the hypothalamus. Increased TXNIP expression was also detected in the liver and adipose tissues of these animals [69]. These studies highlighted physiological functions for TXNIP in regulating energy metabolism.

# 6. Physiological Consequences of Loss of TXNIP

## 6.1. Experimental Animals

A number of studies have reported the phenotypes of mice constructed to have total TXNIP gene deletion. The consequences of this have been both beneficial and detrimental depending on the disease model. In an initial report, the cause of hyperlipidemia in a mutant mouse strain (Hcb-19) was a mutation in the *Txnip* gene resulting in reduced expression. These mutant mice had hypertriglyceridemia, hypercholesterolemia, elevated plasma apolipoprotein B, and increased secretion of triglyceride-rich lipoproteins with increased ketone body synthesis [70]. In a TXNIP gene-deleted mouse model, they developed significantly increased fatty liver, with high levels of triacylglycerol, cholesterol ester, and total cholesterol, with higher-serum non-esterified fatty acids. Elevated fatty acid synthesis was the primary cause of liver lipogenesis in TXNIP knockout mice [71]. Gene deletion of TXNIP also resulted in impaired immunity with reduced numbers of natural killer cells and the impaired dendritic cell maturation of T cells [72][73][74]. TXNIP gene deletion can lead to lethality under fasting conditions due to a switch in metabolism to hyperlipidemia and hypoglycemia. Under these conditions, mice experienced enhanced glucose-induced insulin sensitivity and secretion and an increased expression of PPAR-target genes [75]. TXNIP gene-deletion mice fed a high-fat diet developed significantly greater fat deposits and body mass but with increased insulin sensitivity. This study correlated the loss of TXNIP with the augmented activation of PPAR-γ [76]. These effects on enhanced hyperlipidemia due to TXNIP gene deletion were detrimental to the affected organisms, but beneficial outcomes upon reversing the consequences of diabetes/hyperglycemia were also observed. Knockdown of TXNIP in vitro protected mesangial cells grown under high-glucose conditions from apoptosis and ASK1 and p38 MAP kinase signaling [77][78]. In wild-type and TXNIP knockout mice rendered diabetic with streptozotocin, the TXNIP knockout mice showed significant protection from diabetic nephropathy. The knockout diabetic mice did not show increased thickening of the basal membrane or increased glomerular TGF-β1, collagen IV, and fibrosis was seen in the wild-type mice [79]. Loss of TXNIP provided significant protection in mice fed a HFD, showing significant protection from retinal degeneration and microvascular dysfunction due to reduced activation by the retinal endothelial cells of TXNIP/NLRP3 inflammasome [80]. TXNIP gene-deletion mice have been shown in general to be protected from the vascular consequences of high-fat/obesity or high-sugar diets compared to wild-type mice. In a model that studied the consequence of HFD and TXNIP gene deletion, it was shown that wild-type mice had significantly impaired blood flow and vascular density due to impaired angiogenesis compared to the TXNIP knockout mice. In this model, there was significantly higher IL-1β, increased numbers of infiltrating macrophages, and increased vascular endothelial growth factor (VEGF) expression and VEGF receptor activation in wild-type mice only. The enhanced vascular inflammation was due to the high-fat diet activating the TXNIP/NLRP3 inflammasome, which did not occur in TXNIP knockout mice [81].

## 6.2. Human Subjects

From the above-described experimental studies, the loss of TXNIP in mice has been beneficial in reversing the consequences of hyperglycemia but with a detrimental effect on liver fatty acid metabolism. These animals were constructed with *Txnip* gene deletions, but the loss of TXNIP has been identified in rare genetic cases in human subjects. The published case report covers children of 4, 9, and 13 years of age [82]. This showed that the loss of TXNIP is nonlethal, but the affected subjects show lactic acidosis, low-serum methionine, and impaired oxidative phosphorylation in response to glucose and pyruvate [82]. There are no reports as yet if such individuals are resistant to diabetes or neurodegenerative diseases. These studies demonstrate that the pharmacological lowering of TXNIP levels is unlikely to be associated with significant side effects.

Table 1 lists the most significant studies related to the effects of TXNIP expression in the brain or brain-derived cells. This is a subjective list based on the theme of this article and is proposed to illustrate the different features of TXNIP in interactions with the nervous system.

**Table 1.** Summary of major studies of TXNIP in the brain or brain-derived cells.

| Finding | Reference |
| --- | --- |
| TXNIP induced in cerebellar granular neurons by changes in potassium led to cell death | [54] |
| Glutamate-induced cell death in vivo and in vitro via TXNIP induced expression | [58] |
| TXNIP expression downregulated in vitro in neuronal cells overexpressing mitochondrial ferritin | [83] |

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| TXNIP induction by Aβn microglia resulting in activation inhibited by antioxidant resveratrol | [84] |
| High-fat-diet fed rats had increased expression of TXNIP in astrocytes, retinal endothelial cells, and microglia | [85] |
| Increased TXNIP expression in a rat model of subarachnoid hemorrhage in neurons, astrocytes, and microglia correlated with cell death, which was reduced by inhibiting TXNIP expression | [86] |
| Increased TXNIP expression in a rat model of subarachnoid hemorrhage in neurons, astrocytes, and microglia correlated with cell death which was reduced by inhibiting TXNIP expression | [86] |
| Downregulation of TXNIP in RPE cell line by oxidative stress reduced cell proliferation | [87] |
| Decreased expression of TXNIP in glioma cells correlated with poor patient outcome | [88] |
| TXNIP was immunolocalized to neurons and microglia in normal drosophila and rat brain tissue | [65] |
| Increased neuronal pyroptosis in a rat model of cerebral thrombosis mediated by elevated TXNIP expression and inflammasome activation | [89] |
| TXNIP overexpression in substantia nigra of mice caused the loss of dopaminergic neurons | [90] |
| Increased expression of TXNIP mRNA, protein, and numbers of immunopositive cells in AD brain | [91] |
| Increased TXNIP expression in the brain of an AD mouse model but reduced expression in the spleen | [92] |

## 7. Modulating TXNIP Expression

A number of different classes of agents can modulate TXNIP expression, including PPAR-γ agonists, which include classes of drugs with insulin-sensitizing properties used for treating diabetes [93]. There have been conflicting results on the interactions of PPAR-γ and TXNIP. One study using human kidney proximal tubule cells showed PPAR-γ agonists attenuated high-glucose-mediated TXNIP expression [94], whereas another using human macrophages showed that the PPAR-γ agonist GW929 enhanced TXNIP expression [95]. Using a rat insulinoma cell line INS-1E to represent pancreatic beta cells, it was shown that hyperglycemia activated TXNIP expression and inhibited the activation of AMPK. Activation of AMPK with metformin or aminoimidazole-carboxamide ribonucleotide (AICAR) reduced TXNIP expression, an effect also observed when cells were treated with the lipid palmitate [96]. AMPK activation inhibited glucose-stimulated ChREBP nuclear entry and binding to the TXNIP promoter, thereby inhibiting TXNIP mRNA expression. These investigators also demonstrated that the addition of insulin to high-glucose-treated INS-1E cells reduced TXNIP expression and prevented high-glucose-mediated apoptosis. Treatment of cells with nitric oxide (NO) stimulated insulin secretion and reduced the expression of TXNIP; this effect was reversed when cells were treated with a nitric oxide synthase inhibitor [97]. A recent study showed that insulin-like growth factor-1 (IGF-1) negatively regulated TXNIP expression in vitro and in vivo. Furthermore, this study demonstrated that oxidative stress and glucose-induced TXNIP expression could be reversed by the administration of IGF-1 [98]. The calcium channel blocker verapamil, which is in widespread clinical use for hypertension, has been demonstrated to significantly inhibit TXNIP expression with therapeutic benefits. In an animal model of diabetic cardiomyopathy, three weeks of treatment with verapamil had a significant therapeutic benefit, which correlated with the reduced expression of TXNIP in cardiomyocytes [99]. The mechanism of action of verapamil appeared to be mediated by the enhanced activation of the transcription repressor nuclear factor Y (NPY) [100]. As mentioned above, verapamil was also effective in inhibiting tau phosphorylation in vivo in 5xFAD AD model mice, inhibiting Aβ-induced tau phosphorylation in vitro, and inhibiting the expression of TXNIP and the activation of p38 MAPK [101].

In a recent study, we identified a novel fluorinated derivative of curcumin that was highly effective in reducing stress-induced TXNIP expression. Cellular models examined used the human retinal pigment epithelial cell line ARPE-19, which have high constitutive levels of TXNIP expression, and macrophages derived from the human THP-1 monocyte cell line,

which have lower constitutive expression. In this study, the effectiveness of fluorinated curcumin derivative Shiga Y6 compared to its non-fluorinated derivative Shiga Y5 in reducing TXNIP protein and mRNA expression under constitutive, high-glucose, endoplasmic reticulum stress, and inflammatory activation was demonstrated [102]. This compound was also effective in inducing TRX protein and mRNA levels in these cellular models. These studies demonstrate that derivatized curcumin molecules were more effective than curcumin alone in lowering TXNIP expression. Other studies have shown the effectiveness of curcumin in vitro and in vivo in inhibiting TXNIP expression but at higher doses than we used for testing the fluorinated curcumin compound [102][103]. The effect of curcumin on TXNIP expression appears to be through the activation of AMPK [58][104].

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