Thioredoxin-Interacting Protein (TXNIP)

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Thioredoxin-interacting protein (TXNIP), widely known as thioredoxin-binding protein 2 (TBP2), is a major binding mediator in the thioredoxin (TXN) antioxidant system, which involves a reduction-oxidation (redox) signaling complex and is pivotal for the pathophysiology of some diseases. TXNIP increases reactive oxygen species production and oxidative stress and thereby contributes to apoptosis.

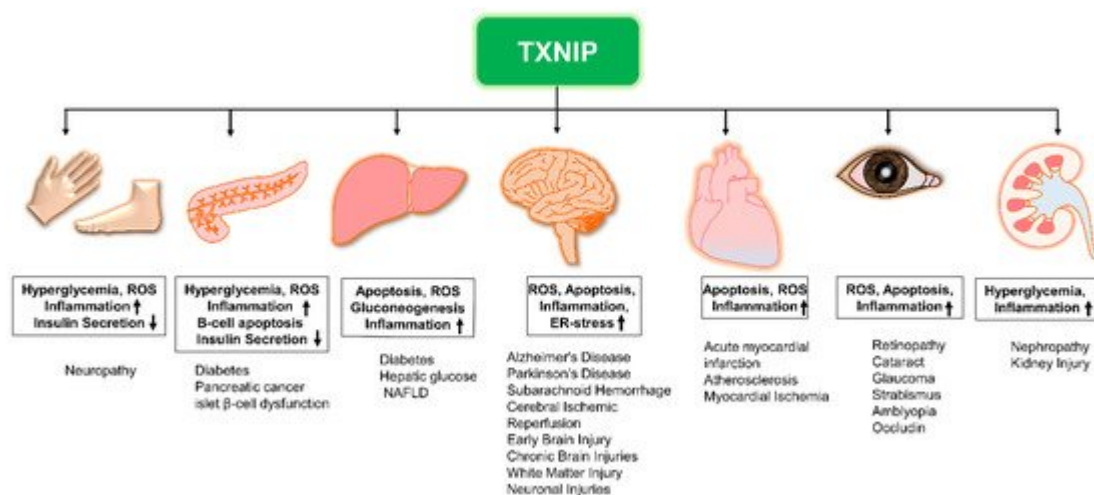thioredoxin   TXNIP   metabolic disorders   neurological disorders   TXNIP modulator

1. The Role of TXNIP in Diseases

1.1. TXNIP in Diabetology

Diabetes mellitus (DM) is a metabolic disorder regulated by a glucose-lowering hormone known as insulin produced by pancreatic β-cells; the release of insulin is not adequate, which results in DM [1][2]. The anomalous reaction of target tissues to insulin-mediated effects, combined with glucose production-promoting hormone glucagon, may enhance aberrant gluconeogenesis leading to hyperglycemic conditions, which predispose to T2DM [3][4]. TXNIP is a prominent regulator of glucose homeostasis through regulating gluconeogenesis in the liver and is implicated in adaptation to acidosis with ATP generation [5]. Although chronic hyperglycemic conditions promote several metabolic vascular complications associated with high death rates in diabetic patients [6], they may include an increase in the formation of advanced glycation end products (AGEs) and ROS [7][8]. Diabetic models show that ROS are not the only factor that promotes DM, but the overall activity of the antioxidant system may be disrupted in DM [9]. TXNIP deletion appears to be pro-oxidant, and reported to lessen the ROS production in vascular smooth muscle cells indirectly implying an increase in the antioxidant potential of TXN in vitro [10]. Moreover, in mouse models of glucose-induced DM, glucose enhances TXNIP expression, which can further induce excessive ROS production in the mitochondria and cytosol. TXNIP is an endogenous inhibitor of the main antioxidant mechanism, i.e., the TXN system, and hyperglycemic conditions have been shown to play a key role in vascular diabetic complications. Upregulated TXNIP is observed in peripheral blood and cultured cells from a diabetic mouse model as well as in pancreatic islets of DM patients [11]. Additionally, TXNIP is important for the promotion of angiogenesis because TXNIP activates and regulates the main angiogenic cytokine known as vascular endothelial growth factor (VEGF). TXNIP overexpression in diabetes regulates the activity of the key cytokine VEGF in a glucose-sensitive manner, whereas a TXNIP knockdown by small interfering RNA (siRNA) can overcome the diabetes-related pathologies of angiogenesis and arteriogenesis and may help to recover an ischemic hindlimb [12]. Moreover, supporting action on islet biology was concurrently revealed in another study through reversion of impaired endothelial cell angiogenic function, generation of VEGF, and sensitivity to VEGF activities [13][7]. Recently, TXNIP-

knockdown has shown improved anti-senescence and anti-inflammation effects on H9c2 cardiomyocytes under doxorubicin-associated cardiomyopathy [14].

Vascular abnormalities in diabetic patients may be attributed to chronic inflammatory responses caused by NLRP3 inflammasome activation. TXNIP also stimulates early apoptotic signals by interacting with inflammation marker, vascular cell adhesion molecule 1 (VCAM-1) in human aortic endothelial cells (HAECs) induced by high-glucose or overexpression of ChREBP, a major transcriptional activator of TXNIP, and impairs nitric oxide (NO) bioactivity; whereas, finally, exaggerated levels of NOs suppress NLRP3 inflammasome activity [7][8][15][16]. Moreover, pyroptosis which is also integrated to the NLRP3 inflammasome activation is associated with diabetes, hypertension, and hyperlipidemia [17]. ERS can control pyroptosis in an alliance of TXNIP with NLRP3 [18]. The literature provides remarkable evidence of elevated ROS and TXNIP levels in diabetic-condition induced NLRP3 inflammasome activation and successive release of caspase 1, IL-1β, and IL-18 (Figure 1). Thus, ROS–TXNIP–NLRP3 inflammasome signaling has a mechanistic link with vascular aberrations in diabetic conditions. The NLRP3 inflammasome directs the obesity-associated danger signal, giving rise to obesity-induced inflammation and insulin resistance. Nevertheless, inhibition of NLRP3 in a mouse model protects against obesity-induced inflammasome activation in the fat-associated pits and liver, and improves insulin signaling [19]. Remarkably, NLRP3 and TXNIP knockout mice show improved glucose tolerance and insulin sensitivity in a T2DM model [18]. Nonetheless, diabetes complications include several complex pathologies, such as nephropathy, retinopathy, neuropathy, ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (macrovascular) (Figure 1).

Figure 1. The role of TXNIP in the development of various diseases. Elevated TXNIP expression may lead to the development of various diseases while contributing to these pathologies via distinct mechanisms. NAFLD: non-alcoholic fatty liver disease; ROS: reactive oxygen species; TXNIP: thioredoxin-interacting protein; Upregulation (↑); Downregulation (↓).

1.1.1. Diabetic Nephropathy (DN)

Diabetic nephropathy is the most common cause of renal disease and is one of the microvascular complications of DM. Patients show associated symptoms such as proteinuria, abnormal blood hemodynamics, glomerulosclerosis, and thickening of the glomerular basement membrane, which is further protected by podocytes and endothelial cells [20][21]. Accumulating evidence suggests that inflammation is a major factor in the pathogenesis of DN [22][23][24]. The primary mechanism of inflammation control is mediated by the upregulation of ROS, which is in turn controlled by the activation of the nuclear factor-κB (NF-κB) pathway and mitogen-activated protein kinase (MAPK) pathway. In addition, ROS act on the TXNIP–TXN complex, thereby causing it to dissociate, and the dissociated TXNIP functions as a ligand that binds and further activates the NLRP3 inflammasome canonically [25]. The importance of the mitochondrial ROS–NLRP3 inflammasome mediated pathway in DN has been inferred from a knockout mouse model [26]. Recently, in vitro and in vivo studies of glucose-induced TXNIP's effects on podocyte apoptosis in a DN mouse model suggested that TXNIP deficiency may reduce podocyte apoptosis by inhibiting mammalian target of rapamycin (mTOR) or MAPK signaling cascades [27]. TXNIP deficiency is characterized by attenuated renal injury in diabetic mice, which means that TXNIP could act as a therapeutic target in DN [27][28].

1.1.2. Diabetic Retinopathy (DR)

In diabetic conditions, high-glucose–induced overexpression of TXNIP leads to early apoptosis of neurons, glial activation, and epithelial retinal pigment injury [29]. Recent in vivo studies showed that in retinal microvascular endothelial cells, inhibition of the ROS-induced TXNIP/NLRP3 cascade by vitamin D3 exerts protective effects against anomalies of retinal structure [30]. Therefore, inhibition of ROS-induced TXNIP production in diabetic mouse models can alleviate the apoptosis of retinal cells just as in DN [27][29].

1.1.3. Diabetic Neuropathy

A serious complication of DM, unfortunately poorly studied to date, is characterized by inflammation and associated with sensation loss in peripheral parts of the body or numbness in extremities, such as feet, and is closely associated with TXNIP [31]. The literature supports the idea that TXNIP/NLRP3-mediated signaling leads to IL-1β and IL-18 activation, resulting in canonical inflammation and worsening of diabetic pathogenesis. In contrast, inhibition of this cascade reduces the apoptosis of neurons and delays neuropathic symptoms in prediabetic patients [18]. Recently, it was demonstrated that NF-κB is a crucial regulator of histone deacetylase 2 (HDAC2) and is involved in neuropathic pain through downstream activation of the TXNIP/NLRP3 inflammasome [32][33]. Furthermore, overexpression of miR-23a in spinal glial cells and miR-183 in microglia has been proposed to relieve neuropathic pain in peripheral body parts [31][34]. Thus, TXNIP might affect diabetic neuropathy by amalgamating inflammation and oxidative stress.

1.2. TXNIP in Neurology

Neurological disorders such as dementia, AD, PD, SAH, and stroke are the most serious diseases of the modern era. Although there are distinct clinical insights into these pathologies, extensive literature suggests that oxidative stress, mitochondrial damage, inflammation, and dysregulated calcium control contribute to the above diseases [35][36][37][38][39][40]. TXNIP is known to link cellular redox events, mitochondrial redox events, and ERS regulation to

pathological inflammation and apoptosis in brain diseases. It also acts as a key mediator in neurodegenerative diseases such as AD and PD [41][42] (Figure 2).

1.2.1. Ischemic/Reperfusion Injury

Ischemic stroke injury is characterized by a blockage in the blood supply to the brain, thereby resulting in sustained deprivation of oxygen supply and leading to brain cell death and damage [43]. TXNIP is overexpressed in ischemic-stroke–induced blood–brain barrier dysfunction and myocardial ischemia/reperfusion injuries [39][44]. TXNIP causes a redox imbalance and leads to inflammasome activation, whereas TXNIP inhibition is an endogenous inhibitor of the thioredoxin system, which helps to reverse ischemic injuries [37]. It has been shown that hypoxic conditions in the ischemic pancreatic cancerous tissue affect the promoter of *TXNIP* and, thus, its transcriptional upregulation, which is equally influenced by HIF-1α [45][46]. Additionally, TXNIP regulates mitochondrial bioenergetics via HIF-1α (an essential regulator of ischemia) modulation in hindering, and peroxisome proliferator-activated receptor 1α (PPAR-1α), as upregulating mitochondrial oxygen consumption [47][48][49]. Nevertheless, the shuttling of cytosolic TXNIP and re-recruitment to mitochondria activates ASK-1, leading to cell death [50]. In the hippocampus, ERS-induced TXNIP/NLRP3-inflammasome activation leads to ischemic neurotoxicity [51]. Moreover, a knockout of *TXNIP* and pharmacological inhibition of TXNIP are reported to protect against brain infarction and neurological diseases in mouse models [52]. So far, the idea to inhibit TXNIP has been elaborated in terms of brain hemorrhage or ischemic stroke, where this protein could serve as a therapeutic target.

1.2.2. TXNIP in Subarachnoid Hemorrhage (SAH)

SAH is a cerebrovascular neurological fatal disorder that reduces brain perfusion and causes bleeding in the space between the brain and the adjacent membrane (subarachnoid space); the major cause of SAH morbidity is early brain injury (EBI) [50]. Elevated levels of *TXNIP* mRNA expression are observed in the patients' brain samples. Furthermore, a rabbit SAH model has been devised, which features elevated TXNIP levels and decreased TXN reductase expression [53]. Concurrent studies have shown that the inhibition of TXNIP via siRNA suppresses apoptosis and alleviates EBI [50]. Recent studies have suggested that ERS induced via PERK and after downstream development of SAH, can initiate EBI by influencing apoptosis [54]. Further research revealed that TXNIP links ERS with neuronal apoptosis, which in turn intensifies EBI [50]. TXNIP interconnects oxidative stress and neuroinflammation to SAH and EBI; as supporting evidence, apelin-13/apelin receptor (APJ) was recently used to reduce EBI via suppressing ERS-associated TXNIP/NLRP3 inflammasome activation and AMP-dependent-protein kinase (AMPK)-dependent oxidative stress following SAH in rats [55]. Furthermore, the white matter injury occurring at the early stage of SAH has not been addressed well so far. Recently, the damage caused by the SAH peroxisome in mouse models was found to escalate white matter injury to SAH, and was partially mediated by TXNIP and glycerone-phosphate acyl-transferase pathways [56].

1.2.3. Alzheimer's Disease (AD)

The involvement of TXNIP in AD is mostly associated with inflammation; accumulated data indicate overexpression of TXNIP in the brain via amyloid-β (Aβ) exposure [57][58], and also TXNIP remained an exclusive marker in

microglia, neurons, astrocytes, and endothelial cells [59]. The prevalent idea proposes that TXNIP is an essential mediator of NLRP3 inflammasome activation and the eventual formation of activated caspase 1 [41]. Preventing the interaction of TXNIP with NLRP3 will, therefore, have positive effects by reversing or restraining AD pathology [42] [60]. Another idea that supports the TXNIP link to AD is glucose control and metabolism associated with neurodegeneration [41]. Although insulin-like metabolic deformities associated with Aβ functions are vague, however, a hypothesized term diabetes type-3 has been suggested recently, for integrated cerebral diabetes, categorizing insulin resistance as independent and overlapping in a few onsets of diabetes with ultimate lack of neuronal response to insulin-related signaling and a decrease in glucose metabolism [61]. Coequal clinical studies confirm that T2DM positive data remained significantly associated with the neuropathology of AD in the presence of ApoE ε4-allele carrier-patients [62]. Epidemiological data validation confirms that insulin-resistant patients are prone to AD-associated dementia and that antidiabetic medication was effective in reducing or reversing risk factors in AD [63]. Recent studies suggest that T2DM (neurovascular-disorder) has not shown any significant correlation with associated biomarkers in mild cognitive disorders in AD, and PD (neurodegenerative-disorders) pathologies [64], although the common biomarkers they tested for reference disorders do not include TXNIP which can be studied in this context. Conversely, it is also suggested that both diseases significantly correlate at early onsets of AD-symptoms [64]. At present, it is an emerging concern since anti-diabetic Food and Drug Administration approved insulin-sensitive drugs are showing positive effects on dementia risk factors via blocking TXNIP expression downstream associated with inflammatory signaling [65][66][67].

1.2.4. Parkinson's Disease (PD)

PD is the second most common neurodegenerative disease among the elderly and includes motor symptoms such as tremors, postural instability, and bradykinesia [68]. PD is characterized by the accretion of filamentous aggregates, with alpha-synuclein (α-syn) as primary precursors, as well as dopaminergic-neuron loss [69][70]. The prevailing theory suggests that the loss of dopaminergic neurons is associated with apoptosis, autophagy, and necrosis [71][72]. Recent data uncovered pyroptosis with a release of proinflammatory cytokines including IL-1β, IL-18, and nuclear protein high mobility group box 1 [73][74]. As pyroptosis is implemented by six conserved domain pore-forming proteins; among them, GSDMD (a gasdermin) is likely cleaved by caspases 11, 4, and 5 in humans [68][75]. It is claimed that pyroptosis is primarily associated with the activation of NLRP3, which is further on upstream is integrated with TXNIP. It has also been confirmed that FOXO1 is upregulated in PD targeted by mi-RNA 135b in MPP+ treated SHSY5y and PC12 cell-lines, whereas the FOXO1–TXNIP–TXN activation cascade interactions have already been confirmed from the perspective of TXNIP regulation [76][77][78]. Additionally, the majority of data highlight the participation of microRNAs and other mediators in PD pathology [79][80]. Recently, downregulation of miR-135b was shown to have a protective effect against PD pathology via promoting FOXO1 upregulation, TXNIP-mediated NLRP3 inflammasome activation, and pyroptosis [79]. TLR4 (Toll-like receptor 4) has an explicit connection to NLRP3 in the presence of myeloid differentiation of primary response protein 88 (MyD88) [81][82]. Many studies have reported improvement in PD symptoms after prevention of NLRP3-dependent pyroptosis. Indirect control inhibits the TLR4–MyD88–NF-κB signaling cascade, thereby reducing the production of NLRP3, pro-IL-1β, and pro-IL-18. The direct approach involves suppression of the TXNIP–NLRP3–caspase 1

signaling cascade [82]. These studies suggest that inhibition of pyroptosis or administration of TXNIP may be a novel therapeutic strategy against PD through direct or indirect NLRP3 activation.

2. TXNIP Is a Potential Therapeutic Target

TXNIP has attracted considerable attention regarding drug development owing to its multiple functions and involvement in metabolic disorders, inflammation, neurodegenerative disorders as well as cancer. Overexpression of TXNIP can be caused by various signals, such as nutritional stimuli, glucose, amino acids, and insulin, suggesting the significance of TXNIP in the regulation of metabolic and neurodegenerative diseases [83][84][85][86]. By contrast, TXNIP being a participant of apoptosis inducer and metabolic re-programmer works as a tumor suppressor; therefore, downregulation of TXNIP contributes to cancer progression [87][88][89][90], although such anticancer functions of TXNIP are associated to apoptotic pathways [91][92]. Thus, TXNIP agonist might help in anticancer treatments, raising yet another debate. In particular, accumulated data provided strong evidence that TXNIP inhibition is a potential therapeutic approach for metabolic disorders and associated diseases [35][93]. On a cellular level under oxidative-stress the metabolic functions of TXNIP are regulated partially independent of TXN1 [94]. So far, there is no specific inhibitor for TXNIP in clinical trials. Efforts are needed to develop novel TXNIP specific inhibitors to de-intensify the pro-oxidant activities of TXNIP. Although, several in vitro and in vivo studies are underway that either antagonize TXNIP directly or block it through extracellular and intracellular signaling by means of inhibitors, such as small-molecule inhibitors, phytochemicals, and peptides (Table 1).

Table 1. Therapeutic modulators of TXNIP. COPD: chronic obstructive pulmonary disease; CTCL: cutaneous T-cell lymphoma; DN: diabetic nephropathy; DR: diabetic retinopathy; HSCs: hematopoietic stem cells; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.

Type	Compound Name	Target	Diseases and Therapeutic Effects	Status	Reference/Clinicaltrials.gov
Small-molecule drug	Verapamil	Calcium channel/TXNIP	T1DM	Phase II	[95][96][97] NCT02372253
			Diabetic cardiomyopathy	In vivo	[98]
	Diltiazem	Calcium channel/TXNIP	Diabetes	In vivo	[95]
	Allopurinol	NLRP3/TXNIP/ ROS/PPARα	Inflammation, diabetes	In vivo	[99]
	Vorinostat	TXNIP	tumors	In vivo	[100]
	Trichostatin A	HDAC/TXNIP	DR	In vivo	[101][102]
	Imatinib	ABL-IRE1α/TXNIP	Diabetes	In vivo	[103]

Type	Compound Name	Target	Diseases and Therapeutic Effects	Status	Reference/Clinicaltrials.gov
	Taurine	Calcium channels/TXNIP	T1DM, T2DM	Phase I/II	[104] NCT01226537
	Metformin	TXNIP	T2DM	In vivo	[105]
	Troglitazone	Trx2/Ask1	Cell injury		[106]
	SRI-37330	TXNIP	Diabetes, obesity	Preclinical	[107]
	Quercetin	NLRP3, TXNIP, ROS, and PPARα	T1DM	Preclinical	[99]
	Fisetin	TXNIP/MAPKs, TLR4/NF-κB, and ROS	Inflammation, antioxidant, anticancer actions	In vivo	[108][109][110]
	Luteolin	TXNIP/NLRP3 inflammasome	antioxidant, inflammation	In vitro	[111]
	Salidroside	TXNIP/NLRP3	T2DM, nephropathy, neuroinflammation, antioxidant	In vivo	[112][113]
	Cepharanthine	TXNIP/NLRP3	anti-inflammatory, DN	In vivo	[114][115]
Phytochemicals	Piperine	TXNIP/NLRP3	anti-inflammatory, DN	In vivo	[115][116]
	Apocynin	NLRP3/TXNIP	Antioxidant, anti-inflammatory, heart problems	In vitro	[117]
	Puerarin	NLRP3/TXNIP	Antioxidant, anti-inflammatory, heart problems	In vitro	[117]
	Curcumin	TXNIP	diabetic vascular inflammation	In vivo	[118]
	Ginsenoside (compound K)	TXNIP/NLRP3	antidiabetic, anti-inflammatory actions	In vitro	[119][120]
Peptides	CB3	p38MAPK/JNK/NF-κB	Neurological diseases,	In vivo	[121][122]

Several small-molecule drugs have been reported, most of which are being used or under clinical investigation for metabolic and neurological disorders. Verapamil and diltiazem, a nondihydropyridine calcium channel blocker, are

Type	Compound Name	Target	Diseases and Therapeutic Effects	Status	Reference/Clinicaltrials.gov
			diabetes, inflammation		
	CB4	p38^{MAPK}/JNK/NF-κB [97]	Neurological diseases, diabetes, inflammation	In vivo	[121][122]
	TN13	TXNIP-p38 [97][125]	Affects aging of HSCs	In vivo	[123]

Other drugs, such as allopurinol and quercetin, have been found to prevent the overexpression of TXNIP in the rat liver and activation of the NLRP3 inflammasome, and upregulation of sterol-regulatory element–binding protein 1c (SREBP-1c), SREBP-2, liver X receptor α (LXRα), fatty acid synthase, and ROS while downregulating PPARα [99]. Moreover, several other small-molecule drugs, for example, telmisartan [126], bakuchiol [127], vorinostat (SAHA) [100], trichostatin A (TSA) [102][128], imatinib [103], taurine [104], and troglitazone [106] can inhibit the expression of TXNIP. Thielen L.A. et al. recently identified a small-molecule inhibitor, SRI-37330, that effectively suppresses TXNIP expression in rats, mice, and human pancreatic islets. In addition, treatment with SRI-37330 reduces glucagon secretion and hepatic glucose production and reverses streptozotocin-induced diabetes [107]. Nonetheless, further studies are warranted to determine the therapeutic window for clinical trials.

Phytochemicals play a major role in the curative effects of plant-derived products on different diseases, including cancers, autoimmune diseases, and neurological and metabolic disorders. Fisetin and luteolin are natural flavonoids found in vegetables and fruits such as apples, grapes, strawberries, onions, and persimmon. Several in vivo studies have revealed that fisetin treatment of mice downregulates proinflammatory cytokines and ROS production and inactivates TXNIP/MAPK and TLR4/NF-κB signaling [108]. Thus, fisetin exerts beneficial effects on the antioxidant system and diabetes-related diseases as well exhibits anticancer activities and anti-inflammatory properties [109][110]. Treatment with luteolin protects podocytes from high-glucose induced apoptosis in the mouse podocyte cell 5 (MCP-5) cell line and blocks TXNIP and NLRP3 inflammasome [129]. Similarly, salidroside suppresses cell proliferation, high-glucose induced oxidative stress, and extracellular-matrix accumulation in rat glomerular mesangial cells (HBZY-1) by inhibiting the TXNIP/NLRP3 signal [112]. Alkaloids such as cepharanthine and piperine are widely used as antineoplastic, antiallergic, and anti-inflammatory agents and are known to ameliorate diabetic neuropathy [114][115], whereas piperine stimulates digestive enzymes and lowers lipid peroxidation [116].

Other phytochemicals have also shown promising effects against different diseases either in vitro or in preclinical models. Among them, metformin [105], apocynin [130], curcumin [131], and ginsenoside (compound K) [120] exert significant beneficial effects on the antioxidant system, inflammation, cancer, DM, and on many other disorders.

Peptides also contribute to inhibiting TXNIP and are useful for the prevention of several disorders (neurological and metabolic disorders). Thioredoxin-mimetic (TxM) peptides, Ac-Cys-Pro-Cys-amide (CB3), and Ac-Cys-Gly-Pro-Cys-

amide (CB4), prevent ROS-related damage by inhibiting p38, MAPK, and c-Jun NH2-terminal kinase (JNK) and by preventing NF-κB nuclear translocation [121][122]. CB3-treated male leptin-receptor-deficient Zucker diabetic fatty (ZDF) rats show lower inflammation and decreased TXNIP/TBP-2 expression. By contrast, the AMPK pathway is activated, which results in the inhibition of the mTOR-p70S6K pathway. Furthermore, CB3 and CB4 induce apoptosis and reduce caspase 3 cleavage and PARP dissociation in human neuroblastoma SH-SY5Y cells. It has been suggested that these peptides may have a potential to prevent neurological disorders and DM [122]. Another peptide, TN13, derived from the TXNIP-p38 interaction motif, inhibits the TXNIP–p38 interaction and significantly revives aged hematopoietic stem cells (HSCs). This finding indicates that the interaction between TXNIP and p38 activates the regulatory mechanism of HSC aging and is a possible therapeutic target for the reactivation of aging HSCs [123].

In recent years, researchers have recognized the role of microRNAs as essential mediators in the control of gene expression via post-transcriptional regulation. Here, we discuss some microRNAs that are potentially relevant for regulating TXNIP and inflammatory diseases (Table 2). MiR-20a negatively regulates the NLRP3 inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes. The overexpression of miR-20a reduces TXNIP expression and downregulates the NLRP3 inflammasome and subsequent secretion of cytokine IL-1β, caspase 1, and matrix metalloproteinase 1 (MMP-1) [132]. Furthermore, the expression of miR-23a is decreased in the blood plasma of patients with central nervous system (CNS) diseases (e.g., ischemic stroke or multiple sclerosis), it also regulates neuropathic pain [133][134]. Besides, downregulation of miR-23a increases chemokine CXC receptor 4 (CXCR4) expression in a neuropathic pain model [34].

Table 2. The miRNAs that regulate TXNIP. ALD: alcoholic liver disease; RA FLS: rheumatoid arthritis fibroblast-like synoviocytes.

miRNAs	Molecular Target	Type of Disease	Molecular Mechanisms	Reference
miR-20a	TXNIP	RA FLS	Downregulation of TXNIP expression; Downregulation of NLRP3, ASC and caspase-1	[132]
miR-23a	CXCR4	Neuropathic pain, multiple sclerosis	Inhibition of CXCR4; Downregulation of the TXNIP/NLRP3 inflammasome	[34][133][134]
miR-377	Not defined	DN, kidney podocyte injury	Increased fibronectin production in diabetic nephropathy; Activation of the p38 MAPK/TXNIP pathway; Upregulation of the NLRP3 inflammasome	[135][136]
miR-17-5p	TXNIP	Retinal inflammation, hypoxia-ischemia	Instability of TXNIP mRNA; Downregulation of the NLRP3 inflammasome	[137][138]
miR-148a	TXNIP	ALD	Reduction of pyroptosis; Downregulation of the NLRP3 inflammasome	[78]

In addition, several other microRNAs have modulatory functions in the pathogenesis of some diseases. For instance, miR-377 overexpression promotes oxidative stress and increases the production of fibronectin in diabetic neuropathy [135][136]. Under stress conditions (ERS), the levels of miR-17-5p decrease, leading to inflammasome activation and causing retinal inflammation [137][138]. In contrast, miR-148a inhibits the expression of TXNIP and prevents the activation of the NLRP3 inflammasome [78]. MiR-33 increases ROS production and regulates the activity of the NLRP3 inflammasome in chronic inflammatory diseases [139].

Major efforts are needed to develop drugs that can specifically inhibit TXNIP and are highly effective in overcoming neurological and metabolic abnormalities.

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