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The Pivotal Role of Thioredoxin-Interacting Protein in Joint Degenerative Diseases

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Abstract

Thioredoxin-Interacting Protein (TXNIP) is a multifaceted protein that regulates oxidative stress (OS) and redox balance by inhibiting the antioxidant protein thioredoxin (TRX). TXNIP also activates the NOD-like receptor family, pyrin domain containing (NLRP3), promoting pro-inflammatory cytokines that exacerbate inflammation. Elevated TXNIP levels promote apoptosis in nucleus pulposus cells and chondrocytes, leading to accelerated tissue degeneration in intervertebral disc degeneration (IVDD) and osteoarthritis (OA) are articular degeneration diseases characterized by the degradation of cartilaginous tissues, primarily driven by oxidative stress, apoptosis, and extracellular matrix (ECM) remodeling. Recently, there has been a growing body of research focused on the mechanisms of TXNIP and its regulation in the OA and IVDD. Importantly, strategies that regulate TXNIP have demonstrated beneficial effects in preclinical experiments. Given the significance and novelty of TXNIP's role in articular degeneration diseases, we present an overview of its mechanisms and discuss its contributions to IVDD and OA. Additionally, we highlight the effectiveness of targeting TXNIP as a valuable strategy for improving our insight into and treatment of degenerative joint diseases.

Keywords: TXNIP, Osteoarthritis, Intervertebral disc degeneration, Oxidative stress, Inflammation

Introduction

Thioredoxin-Interacting Protein (TXNIP) is a multifunctional protein that serves as a crucial modulator of oxidative stress (OS) and cellular redox equilibrium by interacting with thioredoxin as a key antioxidant enzyme [1]. This interaction is essential for preserving cellular homeostasis and reducing oxidative damage [2]. TXNIP has become increasingly significant in recent research as an important factor in the pathophysiology of articular degeneration conditions, specifically osteoarthritis (OA) and intervertebral disc (IVD) degeneration (IVDD) [3,4].

The IVD is a fibrocartilaginous structure situated between vertebral bodies, consisting of 3 primary components: the nucleus pulposus (NP) with cells of chondrocyte, the outer annulus fibrosus (AF), and the cartilaginous endplates (CEP) [5]. The resident NP is tasked with synthesizing proteoglycans and type II collagen, which govern extracellular matrix (ECM) metabolism [6]. The specialized ECM within the IVD is crucial for transferring mechanical loads and enabling spinal movement [7]. TXNIP is involved in various cellular functions, including the regulation of ECM components such as proteoglycans and collagen [8]. When TXNIP is dysregulated, it can interfere with ECM metabolism, resulting in the degeneration of disc tissue and exacerbating pain [9]. Furthermore, TXNIP affects inflammatory pathways, which are increasingly recognized as significant factors in disc degeneration [2]. Elevated levels of TXNIP in NP cells can amplify

inflammatory responses, apoptosis, and compromising the integrity of the disc [10].

Likewise, in OA, TXNIP is associated with inflammatory processes that lead to cartilage degradation and joint dysfunction [3]. Elevated levels of TXNIP have been linked to elevated production of pro-inflammatory cytokines, such as IL-1β and TNF-α, which are crucial in the progression of OA [1,4]. Moreover, TXNIP affects pain perception and overall joint health [11].

IVDD and OA are common degenerative joint disorders that have significant economic impacts on contemporary society [12]. IVDD is a major contributor to chronic lumbar pain, as well as OA is the primary cause of disability among elderly individuals, both of which significantly reduce individuals' quality of life [13-15]. Currently, there are limited methods to slow or reverse IVDD and OA diseases. Recent research aimed to understand the mechanism of IVDD and OA to create effective therapies that can reduce their progression. Although the mechanisms underlying IVDD and OA are intricate, the continuous breakdown of cartilaginous tissue and the impairment of NP cells and chondrocytes are acknowledged as critical factors in the disease progression. Thus, safeguarding NP cells and chondrocytes are crucial for preserving cartilage health and presents a promising therapeutic approach for IVDD and OA [12,16].

TXNIP-induced oxidative stress significantly influences mitochondrial function through various mechanisms. It elevates the production of reactive oxygen species (ROS), which can harm mitochondrial membranes, proteins, and DNA, thereby impairing mitochondrial respiration and ATP synthesis [17]. The oxidative stress that disrupts the mitochondrial membrane potential, resulting in decreased energy availability [17]. Additionally, it can activate apoptotic pathways by stimulating pro-apoptotic factors and inhibiting anti-apoptotic ones, leading to increase mitochondrial permeability and the release of cytochrome c, which activates caspases [3]. Furthermore, oxidative stress disrupts mitochondrial dynamics by altering the balance between fission and fusion, causing fragmented mitochondria and further functional impairment [18]. Moreover, it shifts cellular metabolism toward glycolysis while suppressing oxidative phosphorylation, diminishing energy efficiency, and increasing lactate accumulation. Furthermore, the inflammatory environment created by TXNIP exacerbates oxidative stress and contributing to a vicious cycle that damages mitochondria [19]. Overall, these mechanisms highlight how TXNIP-induced oxidative stress negatively impacts mitochondrial function, potentially exacerbating degenerative conditions such as OA and IVDD.

The TXNIP facilitates the activation of the NF-κB signaling pathway as a key regulator of inflammatory responses. When TXNIP is elevated that enhance the phosphorylation of IκB proteins, resulting in the degradation of IκB and the release of NF-κB dimers, such as p65/p50 [2]. This translocation of NF-κB to the nucleus stimulates the expression of pro-inflammatory cytokines, including TNF-α and IL-6, thereby contributing to the chronic inflammation linked to conditions like OA and IVDD.

However, TXNIP plays a role in the activation of the NLRP3 inflammasome, which is an essential element of the innate immune response [20]. In conditions of OS, TXNIP can associate with NLRP3, promoting its assembly and activation [21]. This process triggers the cleavage and activation of caspase-1, leading to the maturation and release of pro-inflammatory cytokines. The activation of the NLRP3 inflammasome by TXNIP amplifies the inflammatory response and contributes to tissue damage and degeneration [1,22].

Approaches designed to inhibit TXNIP expression or its activity could help reduce the inflammatory processes and oxidative damage linked to these degenerative conditions. Furthermore, gaining a deeper understanding of the specific mechanisms by which TXNIP affects cellular responses in IVDD and OA can offer valuable insights for developing a new treatment strategies aimed at maintaining disc and joint health.

TXNIP is a critical player in the pathology of IVDD and OA, influencing both cellular metabolism and inflammatory responses. As research continues to unfold, targeting TXNIP may offer new avenues for effective interventions in managing these common and debilitating conditions.

Current knowledge about TXNIP in the context of IVDD and OA highlights several areas requiring further investigation. Additionally, the specific

functions of TXNIP in different cell types within the nucleus pulposus and articular cartilage are not well understood, nor its influence on ECM dynamics fully explored. Most existing research is conducted *in vitro*, emphasizing the need for vivo studies to validate these findings and better assess TXNIP modulation in physiological settings. Moreover, there has been limited research into the potential of TXNIP as a therapeutic target, especially in relation to specific inhibitors or modulators. Future studies should aim to clarify the molecular pathways involving TXNIP, conduct longitudinal and comparative studies, and explore the development of TXNIP-targeted therapies.

Utilizing TXNIP as a biomarker for disease progression or treatment response in IVDD and OA holds considerable promise. Elevated TXNIP levels are associated with increased oxidative stress and inflammation, which are critical factors in the advancement of these conditions. Monitoring TXNIP expression could offer valuable insights into disease severity and aid in evaluating the effectiveness of anti-inflammatory or regenerative therapies. Furthermore, alterations in TXNIP levels following treatment may indicate therapeutic efficacy and confirming clinical decisions. However, additional research is necessary to validate TXNIP as a dependable biomarker, establish standardized measurement methods, and correlate its levels with clinical outcomes. If successful, TXNIP could improve personalized treatment approaches in IVDD and OA, enhancing patient management.

This review article presents an overview of TXNIP and outline the existing literature to examine its role in the mechanism of IVDD and OA. Moreover, discuss recent studies, which focused on therapeutic strategies targeting TXNIP mechanisms and emphasizing the potential therapeutic implications for treating degenerative joint diseases.

Data retrieval plan

A thorough computer-based search was performed in the PubMed and Web of Science databases, gathering articles published up to November 30, 2024. The search approach (**Figure 1**) employed a blend of keywords and Medical Subject Headings (MeSH) terms to enhance both the specificity and sensitivity of the retrieval. The keywords included “Thioredoxin-Interacting Protein”, “Oxidative Stress”, “Inflammation in Osteoarthritis”, and “Intervertebral Disc Degeneration”. The retrieved results were subsequently screened based on their titles and abstracts.

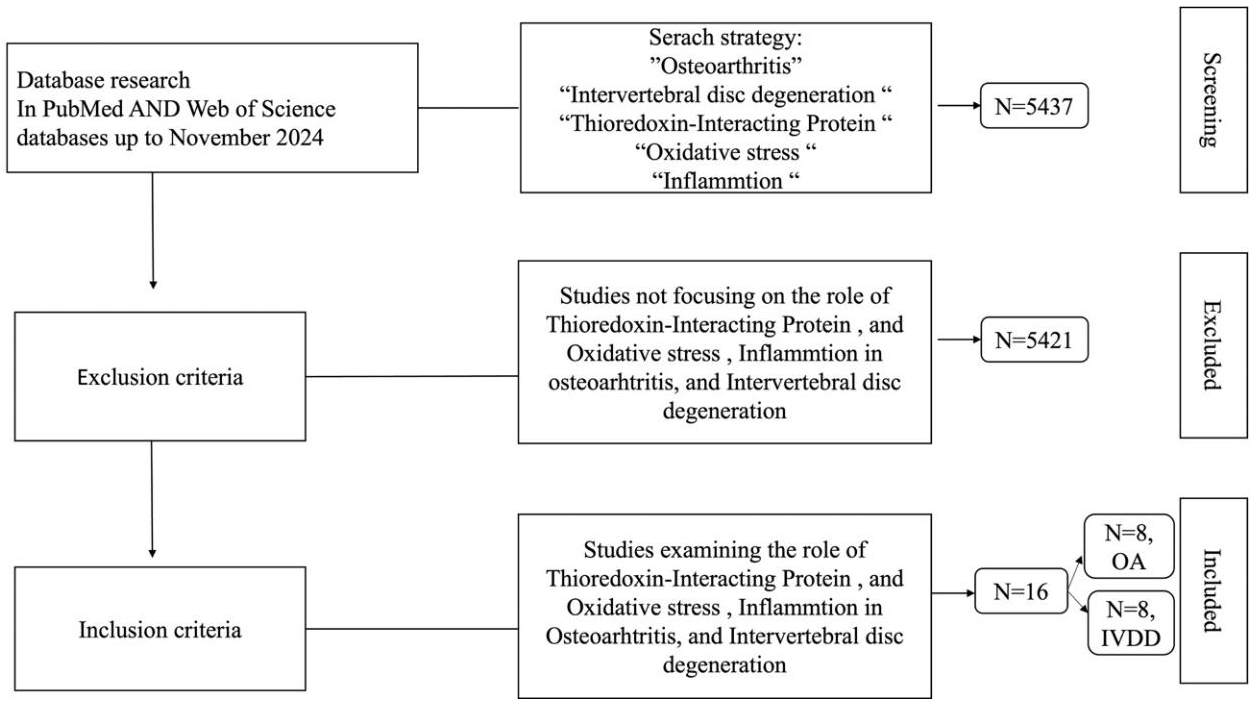

Figure 1 Flow diagram illustrating our research data retrieval plan.

Overview of TXNIP

TXNIP is part of the α-arrestin protein family and features 2 arrestin-like domains: One containing a PxxP sequence and the other a PPxY sequence. Arrestin proteins can attach to photoactivated phosphorylated rhodopsin, preventing it from activating transduction proteins and phosphodiesterase [23]. Along with 5 other proteins referred to as arrestin domain-containing proteins 1 - 5 (ARRDC1–5), TXNIP is categorized as an α-arrestin based on phylogenetic analyses. Although the N and C domains of α-arrestin exhibit similarities to those of β-arrestin, they are characterized by a highly conserved PPxY motif at the C-terminal tail, allowing interaction with the WW domains of proteins such as ubiquitin ligase [24].

One mRNA for TXNIP encodes 336 amino acids, resulting in a polypeptide of approximately 37.4 kDa, while another encodes 391 amino acids, producing a polypeptide of about 43.7 kDa [19]. Reported molecular weights of TXNIP differ based on the expressing cell type; however, the predominant protein band(s) identified by SDS-gel electrophoresis range from 50 to 55 kDa, indicating a degree of post-translational modification [19]. Immunoblots using specific antibodies and cell types have revealed protein bands around 37 kDa, but the 50 to 55 kDa polypeptides are considered the major form.

The PPxY motif is crucial for mediating interactions with proteins like ubiquitin ligases, significantly affecting proteostasis in NP cells and chondrocytes [25]. Acting as a recognition signal for specific ubiquitin ligases, the PPxY motif facilitates the targeting of proteins for ubiquitination and subsequent degradation through the ubiquitin-proteasome pathway [25]. This mechanism is vital for removing misfolded or damaged proteins, thus maintaining cellular health. In NP cells and chondrocytes, regulating protein levels in this manner helps mitigate inflammation and prevent cellular stress, promoting tissue homeostasis [26]. Additionally, proper proteostasis influences various cellular processes, including survival, differentiation, and stress responses, which are essential for the integrity of the extracellular matrix and overall tissue function [27,28]. Disruption of PPxY-mediated interactions can lead to compromised proteostasis, contributing to conditions such as IVDD and OA, where the buildup of damaged proteins worsens inflammation and cellular dysfunction [2,29].

TXNIP’s α-arrestin-like role notably differs from that of other α-arrestins in degenerative joint disorders due to its distinct integration of redox signaling and metabolic regulation [30]. While conventional α-arrestins mainly focus on modulating receptor signaling and desensitization, TXNIP plays a significant role in regulating oxidative stress, linking its function to cellular damage in conditions such as OA. Moreover, TXNIP interacts with key inflammatory pathways, including NF-κB and the NLRP3 inflammasome, positioning it as a crucial component in inflammation-related mechanisms, unlike other α-arrestins that typically do not participate in these processes [2]. Additionally, TXNIP affects cellular metabolism, particularly in glucose sensing and energy homeostasis, thereby influencing the metabolic state of NP cells and chondrocytes [31]. This array of functions highlights TXNIP's complex and multifaceted contributions to degenerative joint disorders, setting it apart from the more receptor-centric roles of other α-arrestins.

TXNIP was initially discovered by multiple researchers as vitamin D3-upregulated protein-1 (VDUP1) in different cell types [32,33]. However, subsequent studies have not consistently confirmed the induction of TXNIP by vitamin D3 in other cell types, and notably, there is no vitamin D3-responsive element in the TXNIP gene promoter. It has been suggested that rather than inducing TXNIP expression, vitamin D3 may stabilize the cellular TXNIP protein [34]. While TXNIP was originally identified as a protein whose expression increased in response to vitamin D3, later studies demonstrated its significant roles in oxidative stress response, inflammation, and metabolism. This broader understanding revealed that TXNIP’s expression is affected by various stimuli, not solely vitamin D3, resulting in inconsistencies in its classification. Reconciling these insights, it is evident that TXNIP's essential functions in managing cellular stress and inflammatory pathways are much more pertinent to health and disease, highlighting the importance of considering TXNIP beyond its initial naming as VDUP1 [32,33].

This review have outlined significant milestones over the past 2 decades regarding the TXNIP regulation interventions of IVDD and OA in both *in vitro/vivo* studies (**Figure 2**).

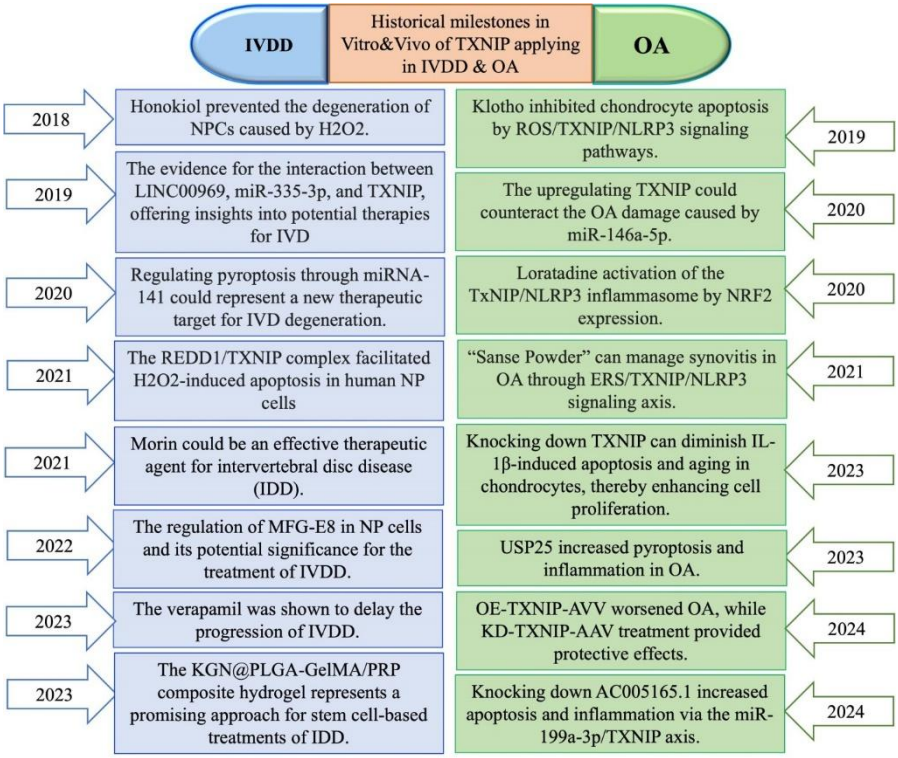

Figure 2 Historical milestones in the application of TXNIP regulation interventions of IVDD and OA in both *in vitro*/*vivo* studies.

Mechanisms of TXNIP in oxidative stress

TXNIP is a key factor in the regulation of OS and cellular redox homeostasis [5]. TXNIP interacts with TRX, a vital antioxidant protein, and implicated in multiple cellular processes, including inflammation, apoptosis, and metabolic regulation [1].

While TRX reduces ROS and serves as a reducing agent for various cellular targets, and can be inhibited by binding to TXNIP [34,35]. Under normal conditions, TRX helps sustain the cellular redox state; however, during oxidative stress, TXNIP levels rise and bind to TRX, impairing its antioxidant function [36].

During OS triggered by factors such as inflammation, disease, or cellular damage levels of ROS rise significantly. In response, TXNIP expression is elevated in different cell types, including immune cells, neurons, and pancreatic cells [34]. TXNIP regulates the cellular response to OS by inhibiting the antioxidant activity of TRX, which results in reduced efficiency in detoxifying ROS and contributes to further oxidative damage.

Moreover, TXNIP plays a key role in the development of various diseases and functions as a critical regulator of the balance between oxidative damage and antioxidant defenses. Targeting TXNIP could provide potential therapeutic advantages in addressing diseases linked to OS [37-39].

TXNIP mechanism in inflammation

TXNIP stimulates the production of pro-inflammatory cytokines, including IL-1β and TNF-α, by activating the NLRP3 inflammasome, which is essential for immune function [40]. The physical interaction between TXNIP and NLRP3 is an integral part of the NLRP3 inflammasome multiprotein complex, which features an adaptor protein referred to as apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) [41]. Nod-like receptors (NLRs) sense internal signals associated with stress, cellular injury, or abnormal cell death, whereas

external signals are connected to pathogens [42,43]. Currently, all known activators of the NLRP3 inflammasome are thought to induce the production of ROS. Additionally, there are several mechanisms for activating the NLRP3 inflammasome; ROS activation from various sources affects the TXNIP–TXN complex, leading to its dissociation. The released TXNIP subsequently activates the NLRP3 inflammasome, resulting in the activation of caspase-1, which triggers the release and maturation of IL-1β and IL-18 [44]. Additionally, TXNIP can trigger pyroptosis that worsens tissue damage during inflammation [45,46]. The dysregulation of TXNIP has been associated with several chronic inflammatory diseases, such as OA and IVDD diseases, highlighting its potential as a therapeutic target [47,48]. **Figure 3** illustrates the TXNIP expression and function may significantly contribute to the etiology mechanism of IVDD and OA.

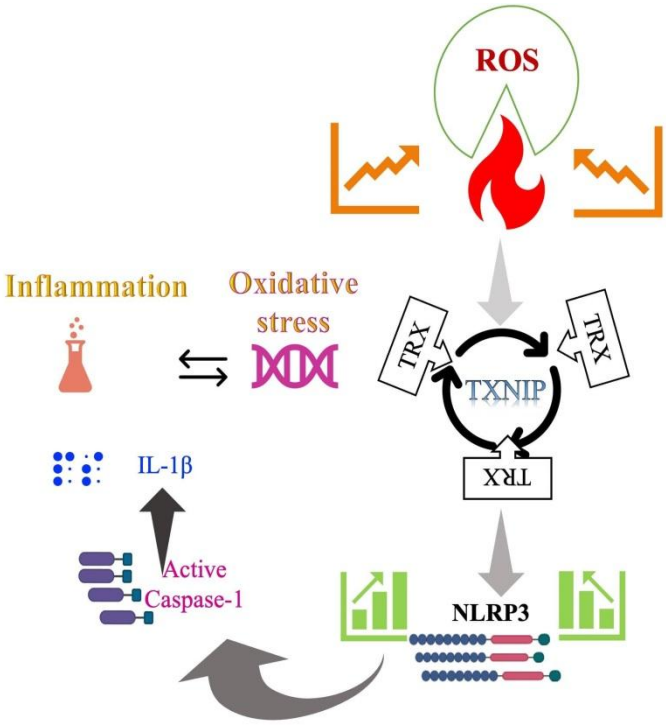

Figure 3 TXNIP expression and function may significantly contribute to the pathogenesis of intervertebral disc degeneration (IVDD) and osteoarthritis (OA). Numerous factors have been identified as potential initiators of degeneration in both conditions. These interactions can lead to increased inflammation and oxidative stress. ROS: Reactive Oxygen Species, TXNIP: Thioredoxin-Interacting Protein, TRX: Thioredoxin, IL: Interleukin, NLRP3: NOD-like Receptor Family, Pyrin Domain Containing.

Role of TXNIP in IVDD

TXNIP that exacerbates the death of NP cells via the ROS/TXNIP/NLRP3/caspase-1/IL-1β pyroptosis signaling pathway when stimulated by TNF-α. Both Morin and milk fat globule-epidermal growth factor 8 have been shown to suppress NP cell pyroptosis and improve IVDD *in vivo* study by reducing the ROS/TXNIP/NLRP3/caspase-1/IL-1β signaling pathway [4,49]. However, Chen Y., found the Nrf2/TXNIP/NLRP3 axis is essential for the protective effects of verapamil. Moreover, it has been observed that verapamil slows the progression of IVDD at both imaging and histological levels [23]. In another study carried out by Tang P., discovered that Honokiol has been demonstrated to inhibit H2O2-induced apoptosis, oxidative stress, and inflammatory responses by down regulating the TXNIP/NLRP3/caspase-1/IL-1β signaling axis, while activating the NF-κB and JNK pathways. This compound exhibits protective properties for NP cells and may be beneficial in

mitigating the pathogenesis of IVDD [50]. As well as Wang F., found the released Kartogenin can promote the differentiation of adipose-derived stem cells into NP-like phenotype and enhance the antioxidant capacity of ADSCs by activating the Nrf2/TXNIP/NLRP3 axis [51]. Moreover, the roles of TXNIP in the mechanisms behind AGE-induced apoptosis of NP cells found silencing TXNIP reduced the impact of advanced glycation end-product on cell viability, apoptosis, and glycolysis in NP cells. In contrast, overexpressing TXNIP led to reduced cell viability, increase in apoptotic cells, and suppression of glycolysis. Furthermore, combination therapy with a glycolysis silencing alleviated the detrimental effects of TXNIP silencing on AGE-induced damage in NP cells. In patients with IVDD classified as Pfirrmann Grades II–V, there were noted increases in TXNIP and advanced glycation end-products (AGEs), along with decreases in GLUT1-4 [4]. Furthermore, AGE levels positively correlated with TXNIP levels, while both AGE and TXNIP exhibited negative correlations with GLUT1-4 [4]. As well as, a previous research found that the regulated in development and DNA damage response 1 (REDD1)/TXNIP enhances OS-induced apoptosis via the mitochondrial pathway, thereby promoting apoptosis in NP cells [52].

However, a study assessed the impact of pyroptosis cell death and identified the crucial miRNAs in IVD by targeting ROS generation and activating the TXNIP/NLRP3 pathway, it was found that an inhibitor of miR-141 significantly reduced ROS generation and the expression level of NLRP3 and TXNIP. Furthermore, the miR-141 inhibitor shown to inhibit IVD degeneration in animals' study [53]. Yu L., LINC00969 was found to be highly expressed, whereas miR-335-3p was significantly reduced in the NP tissues and cells of patients with IVDD. In addition, LINC00969 was identified as a competing endogenous RNA (ceRNA) for miR-335-3p, thereby enhancing TXNIP expression in cells study [54]. This study summarized key examples of vitro and vivo applications of TXNIP regulators in IVDD disease (**Table 1**).

Significant breakthroughs in understanding TXNIP regulation in IVDD include its recognition as a crucial regulator of OS in NP cells, where elevated TXNIP levels result in increased production of ROS, contributing to cellular damage. Research has also clarified TXNIP's role in inflammatory pathways, particularly the interactions with NF-κB and the NLRP3 inflammasome, which exacerbate chronic inflammation and tissue degeneration in IVDD. Furthermore, TXNIP affects metabolic functions, such as glucose metabolism and energy homeostasis, which are vital for NP cell health. Its involvement in mechanotransduction has been emphasized, revealing how mechanical stress influences NP cell function and degeneration. Additionally, TXNIP is being investigated as a therapeutic target to alleviate oxidative stress and inflammation, while its potential as a biomarker for disease progression provides insights into severity and treatment response. Together, these discoveries have greatly enhanced the understanding of TXNIP's regulatory roles in IVDD, paving the way for new research and therapeutic approaches.

Role of TXNIP in OA

TXNIP plays an important role in the pathogenic mechanisms of OA through its involvement in OS and inflammatory processes. In Xu et al., indicated that the expression of TXNIP in chondrocytes increased proportionally with varying ratios of IL-1β. Silencing TXNIP using shRNA led to enhanced cell proliferation, reduced chondrocyte apoptosis, and diminished signs of chondrocyte aging. Additionally, the expression of genes such as Col 2a, TNF, IL-6, matrix metalloproteinases (MMP), and ADAMTS-5, as well as associated protein levels, showed a relative decrease [3,13]. Notably, the expression of the upstream- associated protein P-ERK remained largely unchanged upon TXNIP silencing, while the amounts of downstream proteins NLRP3 and Caspase-1 were slightly decreased. Silencing TXNIP can effectively reduce IL-1β-induced chondrocyte apoptosis and aging, while stimulating cell proliferation [37]. In Altahla et al., examined the TXNIP roles in the activation of the NLRP3 via the pyroptosis pathway in DMM rats model, found OA+intra-articular injection of overexpression-TXNIP led to joint structural damage, reduced expression of anabolic proteins, and increased levels of catabolic proteins and pyroptosis factors. In contrast, knock down-TXNIP treatment reduced the OA progression. While overexpression - TXNIP exacerbated OA by increasing joint

degeneration, knock down-TXNIP demonstrated a defensive effect [3]. Study focusing on the miR-199a-3p/TXNIP axis discovered that knocking down AC005165.1 led to increased apoptosis and inflammation in chondrocytes treated with IL-1β [54], while the miR-146a-5p/TXNIP was shown to inhibit cell proliferation and promote apoptosis in OA cartilage injury [55]. Additionally, the animal study demonstrated that the levels of TRX family members and the anti-aging protein Klotho are diminished, resulting in apoptosis and IL-1β release in the OA mice. These effects are reversed by the overexpression of Klotho via blockade of TXNIP and pyroptosis-related molecules, such as NLRP3 and caspase-1[60]. Furthermore, research on the pyroptosis pathway revealed that USP25 enhances ROS production, activating the NLRP3 inflammasome through TXNIP, which leads to increased pyroptosis and inflammation in OA [56]. However, another animals research demonstrated that a nanoemulsion of essential oil (Sanse Powder) decreased the expression level of the ERS/TXNIP/NLRP3 axis pathway, as well as the levels of IL-1β and IL-18, thereby alleviating the inflammatory of synovial and providing OA theraputic [57]. Loratadine reduces the expression level of TXNIP and components of the NLRP3, for example (NLRP3, ASC, and caspase-1), by suppressing the production of mitochondrial ROS. This effect helps mitigate SW1353 chondrocyte injury caused by AGEs. Furthermore, loratadine decreases Nrf2 expression; however, when Nrf2 expression is silenced, the inhibitory effect of loratadine lost the activate of NLRP3. Therefore, loratadine protects chondrocytes from AGE-induced TXNIP/NLRP3 activation by regulating Nrf2 expression level, which contributes to the alleviation of OA [58]. Despite these insights, the understanding of TXNIP's molecular mechanisms, particularly concerning the pyroptosis pathway in OA, remains underexplored, warranting further investigation to explore its potential as a therapeutic target. We have summarized key examples of vitro and vivo applications of TXNIP regulators in OA disease (see **Table 1**).

Significant breakthroughs in understanding TXNIP regulation in OA include its recognized role in inflammatory processes, where it interacts with crucial pathways such as NF-κB and the NLRP3 inflammasome, enhancing the production of pro-inflammatory cytokines that contribute to joint inflammation and degradation. Additionally, TXNIP has been identified as a vital regulator of OS in chondrocytes, with increased levels linked to elevated ROS production, resulting in cellular damage and worsening degenerative processes. Research has also demonstrated TXNIP's role in regulating MMPs, enzymes that are instrumental in cartilage degradation, directly affecting cartilage breakdown. Furthermore, TXNIP is involved in metabolic regulation within chondrocytes, particularly related to glucose metabolism and energy homeostasis, which are essential for maintaining cartilage health. As a potential therapeutic target, TXNIP is being investigated for its capacity to modulate inflammation and OS, and its recognition as a biomarker for OA progression provides valuable insights into disease severity and treatment efficacy. Collectively, these discoveries have greatly enhanced the understanding of TXNIP's regulatory functions in OA, opening new avenues for research and therapeutic interventions.

Table 1 Application of TXNIP regulators in IVDD, OA diseases.

Intervention	Mechanism	Disease	Status	Main outcomes	Reference
MFG-E8	Nrf2/TXNIP/NLRP3 axis	IVDD	*Vitro/ Vivo*	The findings uncovered the internal mechanisms involved in MFG-E8 regulation in NP cells and highlighted its potential significance for the treatment of IVDD.	[9]
Morin	TXNIP/NLRP3/Caspase-1/IL-1β signaling pathway	IVDD	*Vitro/ Vivo*	TXNIP promotes pyroptosis in NP cells through the NLRP3/Caspase-1/IL-1β signaling pathway. Morin significantly inhibited the TXNIP/NLRP3/Caspase-1 pathway *in vitro*. *In vivo*, our data indicate that TXNIP exacerbates intervertebral disc degeneration, while morin may serve as an effective therapeutic agent for	[51]

Intervention	Mechanism	Disease	Status	Main outcomes	Reference
				intervertebral disc disease.	
Verapamil	Nrf2/TXNIP/NLRP3 axis	IVDD	*Vitro/ Vivo*	The Nrf2/TXNIP/NLRP3 axis is crucial for the protective effects of verapamil. *In vivo*, verapamil was shown to delay the progression of IVDD.	[52]
Honokiol	TXNIP/NLRP3/caspase-1/ Interleukin - 1β signaling axis	IVDD	*Vitro/ Vivo*	Honokiol prevented the degeneration of nucleus pulposus cells caused by H2O2. The H2O2 triggered the activation of the TXNIP-NLRP3 axis in these cells. Honokiol inhibited the H2O2-induced activation of the TXNIP-NLRP3 axis. Additionally, honokiol alleviated intervertebral disc degeneration in a rat model induced by puncture.	[23]
Kartogenin-loaded hydrogel	Nrf2/TXNIP/NLRP3 axis	IVDD	*Vitro/ Vivo*	The KGN@PLGA-GelMA/PRP composite hydrogel, when combined with adipose-derived stem cells, reduced the degeneration of rat intervertebral discs *in vivo*. Additionally, KGN promotes the differentiation of ADSCs and enhances their antioxidant capacity by activating the Nrf2/TXNIP/NLRP3 axis.	[50]
REDD1/TXNIP Complex	Mitochondrial pathway	IVDD	*Vitro/ Vivo*	The simultaneous inhibition of the REDD1/TXNIP complex proved more effective than inhibiting either REDD1 or TXNIP alone in promoting cell proliferation and enhancing apoptosis. Additionally, p53 serves as the transcription factor for REDD1, regulating the REDD1/TXNIP complex in response to oxidative stress. Overall, our findings indicate that the REDD1/TXNIP complex mediates H2O2-induced apoptosis in human nucleus pulposus cells and contributes to intervertebral disc degeneration through the mitochondrial pathway.	[51]
miRNA-141	TXNIP/NLRP3 Signaling	IVDD	*Vitro/ Vivo*	miRNA-141 was found to be significantly upregulated in degenerated nucleus pulposus tissue. The use of a miR-141 mimic inhibited the matrix synthesis function of NPCs. In contrast, an miR-141 inhibitor significantly reduced the generation of reactive oxygen species as well as the expression of TXNIP and NLRP3. Additionally, the miR-141 inhibitor effectively prevented intervertebral disc degeneration *in vivo*.	[52]
LINC00969	miR-335-3p /NLRP3 inflammasome	IVDD	*Vitro/ Vivo*	LINC00969 increased apoptosis in nucleus pulposus cells. Notably, it was identified as a competitive endogenous RNA (ceRNA) for miR-335-3p, which positively regulates TXNIP expression *in vitro*.	[53]
Blocking TXNIP	TXNIP/ IL-1β signaling pathway	OA	*Vitro/ Vivo*	Silencing TXNIP can reduce IL-1β-induced chondrocyte apoptosis and aging, promoting cell proliferation.	[54]
Blocking/ overexpression TXNIP	TXNIP/NLRP3 Signaling	OA	*Vivo*	OE-TXNIP-AVV exacerbated OA by accelerating joint degeneration and damage, whereas KD-TXNIP-AAV treatment offered protective benefits.	[3]
LncRNA AC005165.1	miR-199a-3p/TXNIP Axis	OA	*Vitro*	Knockdown of AC005165.1 enhanced apoptosis and the inflammatory response in IL-1β-treated chondrocytes through the miR-199a-3p/TXNIP axis.	[54]
miR-146a-5p	TXNIP/ IL-1β signaling pathway	OA	*Vitro*	The expression of miR-146a-5p was increased in SW1353 and C28/I2 cells upon stimulation with IL-1β. Silencing miR-146a-5p notably improved cell activity, decreased the expression of inflammatory factors, and reduced cell apoptosis.	[55]
Klotho	ROS/TXNIP/NLRP3 signaling pathways	OA	*Vitro/ Vivo*	The expression level of Klotho was noticeably reduced in the articular cartilage of OA mice. Moreover, it was observed that mechanical loading significantly	[56]

Intervention	Mechanism	Disease	Status	Main outcomes	Reference
				decreased both the expression and activity of Klotho in chondrocytes. Additionally, the overexpression of Klotho inhibited chondrocyte apoptosis by modulating the thioredoxin/peroxiredoxin (Trx/Prx) family and the ROS/TXNIP/NLRP3 signaling pathways.	
Ubiquitin-specific peptidase 25 (USP25)	TXNIP/NLRP3 signaling pathways	OA	*Vitro/ Vivo*	USP25 induced excessive ROS production, which activated the NLRP3 inflammasome by regulating TXNIP, leading to heightened pyroptosis and inflammation in OA.	[57]
essential oil nanoemulsion (Sanse Powder)	ERS/TXNIP/NLRP3	OA	*Vivo*	GC-MS analysis identified 30 compounds in SP-EO and 11 in NEs-SP-EO, which showed suitable particle size, negative charge, and stability. *In vitro* and vivo, NEs-SP-EO exhibited anti-synovitis efficacy by reducing the ERS/TXNIP/NLRP3 signaling axis and regulating the overproduction of IL-1β and IL-18.	[58]
Loratadine	TXNIP/NLRP3, ROS, Nrf2	OA	*Vitro*	Loratadine reduced AGEs-induced oxidative stress by decreasing mitochondrial ROS and NOX4 levels. It inhibited TxNIP and components of the NLRP3 inflammasome, including NLRP3, ASC, and cleaved caspase 1 (P10). Furthermore, loratadine suppressed NRF2 expression, and silencing NRF2 negated its inhibitory effect on NLRP3 inflammasome activation.	[59]

Conclusions and future perspective

OA and IVDD are degenerative joint diseases closely linked to aging. They exhibit similar pathological mechanism, like as mitochondrial dysfunction, OS, and inflammation [59]. TXNIP's effects vary significantly between cartilage and IVD tissues due to differences in cellular composition, mechanical environment, and metabolic requirements [50]. In cartilage, TXNIP primarily affects chondrocytes, promoting inflammation and apoptosis, which contribute to cartilage degradation and OA [18]. Conversely, in IVD tissue, TXNIP influences NP cells, regulating ECM metabolism; its dysregulation can lead to IVDD and pain [60,61]. The mechanical loading experienced by cartilage can intensify OS and inflammation through TXNIP, worsening degeneration, while the unique mechanical demands of the IVD necessitate TXNIP's role in maintaining hydration and nutrient transport for disc function. Furthermore, elevated TXNIP levels in both tissues increase pro-inflammatory cytokine production, but the specific biological responses reflect the distinct functions of TXNIP in these contexts [18]. In summary, TXNIP is crucial in the progression of both IVDD and OA, primarily by regulating OS and inflammation. Increased levels of TXNIP are linked to heightened apoptosis and inflammatory responses in NP cells and chondrocytes, leading to the deterioration of cartilage and disc tissue. The protein's interaction with the NLRP3 inflammasome and its impact on critical signaling pathways highlight its importance in these degenerative conditions. However, there were several shared therapeutic strategies can be applied to IVDD and OA, focusing on reducing inflammation, promoting tissue repair, and managing pain. Anti-inflammatory treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, can alleviate pain and inflammation in both conditions [62]. Biologic therapies, including platelet-rich plasma (PRP) and stem cell treatments, promote tissue regeneration and enhance extracellular matrix production [61-65]. Gene therapy targeting specific inflammatory pathways, such as TXNIP, may also be beneficial. Additionally, physical therapy and rehabilitation improve mobility, while nutritional interventions like glucosamine and chondroitin sulfate support cartilage and disc health. Modulating OS with antioxidants can help combat degeneration in both tissues. Lastly, regenerative approaches like IVD replacement can draw on methodologies used for joint repair in OA. By leveraging these strategies, clinicians can develop comprehensive treatment approaches that

address the underlying mechanisms of both IVDD and OA, improving patient outcomes.

Future studies should aim to clarify the specific molecular mechanisms through which TXNIP exerts its effects, especially in relation to the pyroptosis pathway. Gaining insights into the regulation of TXNIP expression and its interactions with other cellular factors could pave the way for innovative therapeutic strategies designed to slow the progression of IVDD and OA.

Future research should focus on elucidating the molecular mechanisms of its role in OS and inflammation, particularly its stimulation of the NLRP3 and pyroptosis pathways. The mechanism by which TXNIP increases OA and IVDD through ferroptosis remains to be explored. Moreover, further research is needed to understand TXNIP's role in autophagy and ER stress in OA and IVDD. Developing specific TXNIP inhibitors could provide novel therapeutic strategies to mitigate disease progression, while exploring combination therapies with existing treatments may enhance efficacy. Investigating TXNIP as a potential biomarker for early diagnosis and prognosis, alongside examining the regulatory roles of microRNAs and epigenetic factors, could further enrich our understanding. Additionally, translational research through animal models and clinical trials is essential to assess the therapeutic impact of TXNIP modulation, with implications that may extend to other degenerative conditions. Gene therapy targeting TXNIP pathways holds potential, but translating these approaches from preclinical models to human applications requires rigorous safety and efficacy evaluations. Overall, this multifaceted approach could significantly advance the management of IVDD and OA, improving patient outcomes and quality of life. Possible intervention strategies could involve the creation of TXNIP inhibitors or modulators that help diminish OS and inflammatory responses, thereby protecting cartilage health and enhancing patient outcomes.

Targeting TXNIP in therapeutic interventions poses several potential limitations, particularly concerning specificity and the risk of adverse effects. TXNIP is implicated in various cellular processes, including OS regulation, inflammation, and metabolism, which suggests that strategies aimed at altering its levels or activity may unintentionally affect other signaling pathways, resulting in unintended consequences. Moreover, TXNIP interacts with multiple proteins and pathways, such as thioredoxin and the NLRP3 inflammasome, and disrupting its function could disrupt critical processes like apoptosis and immune responses. Variability in TXNIP expression across individuals and different tissues may also influence the effectiveness of TXNIP-targeting therapies. Additionally, the long-term consequences of chronic modulation of TXNIP are not well understood, possibly leading to compensatory mechanisms that undermine therapeutic benefits. Concerns about off-target effects and the potential for cells to develop resistance over time further complicate the effectiveness of these strategies. Collectively, these limitations emphasize the need for careful consideration and further investigation to ensure the safe and effective use of TXNIP-targeting therapies.

However, investigating the therapeutic potential of targeting TXNIP alongside other pathways implicated in IVDD and OA may produce synergistic effects, increasing the overall efficacy of treatment approaches. Given the increasing incidence of these conditions and their significant impact on quality of life, further research into TXNIP as a therapeutic target holds great promise for improving our understanding and management of degenerative joint diseases.

The key points summarizing the findings

- TXNIP is crucial in the progression of both OA and IVDD, linking them to aging and shared pathological mechanisms like mitochondrial dysfunction, OS, and inflammation.
- TXNIP's effects vary between cartilage and IVD tissue due to differences in cellular composition and metabolic needs. In cartilage, it promotes inflammation and apoptosis in chondrocytes, while regulates extracellular matrix metabolism in NP cell in IVD.
- Elevated TXNIP levels in both tissues lead to increased production of pro-inflammatory cytokines and exacerbating degeneration.
- TXNIP interacts with the NLRP3 inflammasome, highlighting its significance in inflammation-related processes in OA and IVDD.

- Shared therapeutic approaches include anti-inflammatory treatments, biologic therapies, and nutritional interventions aimed at managing symptoms and promoting tissue repair.
- Further investigation is needed into TXNIP's molecular mechanisms, particularly regarding pyroptosis, ferroptosis, autophagy, and ER stress.
- Developing specific TXNIP inhibitors could offer new therapeutic options, and exploring TXNIP as a biomarker may improve early diagnosis and prognosis.
- Targeting TXNIP presents challenges related to specificity and potential adverse effects, as it is involved in multiple cellular processes, which may lead to unintended consequences.
- Investigating TXNIP alongside other pathways may enhance treatment efficacy for OA and IVDD.
- Given the increasing incidence of these conditions, further research into TXNIP as a therapeutic target is essential for improving management and patient outcomes.

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