The role and mechanism of TXNDC5 in disease progression

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Thioredoxin domain containing protein-5 (TXNDC5), also known as endothelial protein-disulfide isomerase (Endo-PDI), is confined to the endoplasmic reticulum through the structural endoplasmic reticulum retention signal (KDEL), is a member of the PDI protein family and is highly expressed in the hypoxic state. TXNDC5 can regulate the rate of disulfide bond formation, isomerization and degradation of target proteins through its function as a protein disulfide isomerase (PDI), thereby altering protein conformation, activity and improving protein stability. Several studies have shown that there is a significant correlation between TXNDC5 gene polymorphisms and genetic susceptibility to inflammatory diseases such as rheumatoid, fibrosis and tumors. In this paper, we detail the expression characteristics of TXNDC5 in a variety of diseases, summarize the mechanisms by which TXNDC5 promotes malignant disease progression, and summarize potential therapeutic strategies to target TXNDC5 for disease treatment.

1 Introduction

The thioredoxin domain containing protein-5 (TXNDC5), also known as ERP46 (1), HCC-2, STRF8, PDIA15, UNQ364, endo PDI, is a member of the PDI family that is located on chromosome 6p24.3. Full-length cDNA analysis indicated that TXNDC5 is a 48 kDa protein measuring 845.2 kbp. It can encode five splice variants, of which TXNDC5-001 and TXNDC5-003 can be translated into proteins (2). TXNDC5 is widely distributed across tissues, mainly in the brain, spleen, lung, liver, kidney, pancreas, testis and others. TXNDC5 is highly expressed in endothelial cells and in the endothelium of tumors and atherosclerotic plaques, and TXNDC5 is upregulated in hypoxic conditions (1, 3–5). It is also upregulated in autoimmune diseases such as rheumatoid arthritis and highly expressed

in various organ fibrosis diseases. Previous studies have shown that TXNDC5, like other PDI family members, regulates disulfide bond formation and rearrangement through the CxxC motif and assists in the proper folding of oxidized residue disulfide bonds (5–7). TXNDC5 functions as a stress survival factor and is required for endothelial cell survival under hypoxic conditions (3). TXNDC5 can mediate tumor necrosis factor-α (TNF-α) induced angiogenesis (8). TXNDC5 can bind to lipocalin receptor 1 as a cellular adapter and participate in cellular metabolism and inflammatory responses by activating downstream inflammatory factors (9). TXNDC5 can bind to alpha -mannosidase–like protein 3 (EDEM3) and trigger the mannose trimming activity of ER degradation to correct misfolded proteins (10). In addition, TXNDC5 also plays a molecular chaperone role and act synergistically with HSC70 to promote inflammation through NF-κB signal transduction (11). The association between TXNDC5 and disease susceptibility has been extensively reported, and multiple SNP across the TXNDC5 locus are closely associated with disease development (Table 1). In this review, we focus on the role of TXNDC5 in various diseases and discuss possible TXNDC5 applications for "TXNDC5-related diseases" particularly cancer, rheumatoid and fibrotic diseases.

2 Structure of the TXNDC5 protein

TXNDC5 is a special member of the PDI family. 40 years ago, it was the first-discovered dithiol-disulfide oxidoreductase, and it is capable of reducing, oxidizing and isomerizing disulfide bonds (17). PDI family proteins consist of four Trx-like structural domains (a, b, b′ and a′) located at the N-terminus and an additional α-helix c structural domain at the C-terminus (18). Together, they form a highly conserved U-shaped structure (19), with each domain connected by an unusually long flexible loop (20). The a and a′ structural domains are redox active due to the Cys-Gly-His-Cys motif and can act synergistically to promote the formation of natural disulfide bonds through the two oxidation sites (20). The b and b′ structural domains lack the Cys-Gly-His-Cys motif, leading to loss of redox activity. However, they are the main substrate binding sites (21–23) and can bind to different substrates through conformational changes (22, 24, 25) (Figures 1A, B). Unlike a prototypical PDI protein, TXNDC5 is a rare PDI containing the conserved APWCGHC thioredoxin domain but no b-structural domain (2, 18, 26). The C-terminus of TXNDC5 protein has an endoplasmic reticulum retention signal (KDEL), which is responsible for protein localization to the endoplasmic reticulum. TXNDC5 consists of three redox-like Trx domains (Trx1, Trx2 and Trx3), which form a clover-like structure (25). Each isolated Trx-like structural domain can rapidly import disulfide bonds independently and in a disorderly manner at the same rate as native TXNDC5 without selectivity (18, 27) (Figures 1C, D). Each Trx domain contains a CGHC motif as the catalytic domain for PDI activity. In contrast, PDI introduces natural disulfide bonds in an orderly manner through the synergistic action of two redox active sites and selectively proofreads unnatural disulfide bonds. TXNDC5 promote the formation and folding of disulfide bonds through the CxxC motif

to enhance protein stability (6, 28). Moreover, TXNDC5 generates H_2O_2 through interaction with PDI endoplasmic reticulum oxidoreductase 1α (Ero1α) to participate in the catalytic oxidation reaction between peroxisomal protein 4 (prx4) and TXNDC5, thereby accelerating protein folding (29). Prx4 is typical of the 2-Cys Prx family (30, 31) and forms a homodecamer within which each dimer constitutes a key functional unit (32, 33). Sato Y et al. also demonstrated that TXNDC5 and other PDI family members can collaborate in peroxiredoxin 4-driven oxidative protein folding to increase the rate and fidelity of oxidized protein folding (27).

3 TXNDC5 is involved in the inflammatory response

Sepsis is a fatal immune disorder (34, 35), excessive immune responses often result in systemic hypoperfusion, tissue hypoxia, and ultimately organ dysfunction (36, 37). Sepsis triggers the production of multiple pro-inflammatory and anti-inflammatory factors (38). Increased release of pro-inflammatory cytokines leads to dysregulated immune responses (39). Multiple pro- and anti-inflammatory factors including TNF-α, IL-1, IL-6 IL-8, IL-12, interferon (INF)-γ, granulocyte colony-stimulating factor (G-CSF), and the anti-inflammatory cytokine IL-10. Among them, TNF-α and IL-1 are considered to be the main pro-inflammatory factors (40–42). TNF-α activates inflammatory cytokines encoded by the NF-κB signaling pathway, adhesion molecules, gene expression of prostaglandin-synthesizing pathway enzymes, and induction of nitric oxide synthase (iNOS), which activates endothelial cells and leukocytes and exacerbates inflammatory responses (43–47). TXNDC5 was found to be upregulated in lipopolysaccharide (LPS) induced sepsis. Further research has found that inhibition of TXNDC5 attenuated-induced sepsis by suppressing the NF-κB signaling pathway. Moreover, knockdown of TXNDC5 effectively inhibited LPS-induced upregulation of pro-inflammatory cytokines (TNFα, IFN-γ, IL-12, IL-6, and MCP-1) and facilitated the production of the anti-inflammatory cytokine IL-10 (48).

In the development of rheumatoid arthritis (RA), TNF-α, IL-1, IL-6, IL-2 and many other inflammatory factors mediate the inflammatory response (49–52). TXNDC5 can also regulate a variety of cytokines to promote the development of the disease. Wang et al. found that in the presence of LPS, the NF-κB signaling pathway was activated by various pro-inflammatory factors such as IL-6, IL-8 and TNF-α, then induced the expression of TXNDC5, in turn, high expression of TXNDC5 can promote the production of pro-inflammatory factors such as IL-6, IL-8 and TNF-α (11); miR-573 can alleviate inflammation by enhancing the expression of TXNDC5, which in turn inhibits the expression of factors such as toll like receptor 2 (TLR2) and epidermal growth factor receptor (EGFR) (53). Highly expressed TXNDC5 can promote RA by inhibiting C-X-C motif chemokine ligand 10 (CXCL10) (54).

Inflammation often induces fibroblast recruitment and fibrosis, and several inflammatory factors, including TGF-β, IL-13, CD4, have been identified as triggers of fibrosis (55). For example, the

TABLE 1 TXNDC5 SNPs and disease susceptibility.

Disease susceptibility	SNPs	Gene: Consequence	Ref
Cervical carcinoma	rs408014, rs7771314	BLOC1S5-TXNDC5: Intron Variant, TXNDC5: Intron Variant	(12, 13)
Liver cancer	rs13210097	BLOC1S5-TXNDC5: Intron Variant, PIP5K1P1: Non Coding Transcript Variant	(13)
	rs11754300	BLOC1S5-TXNDC5: Intron Variant, PIP5K1P1: Non Coding Transcript Variant	
	rs9392182	BLOC1S5-TXNDC5: Intron Variant	
	rs2815128	BLOC1S5: Intron Variant, BLOC1S5-TXNDC5: Intron Variant, EEF1E1-BLOC1S5: Intron Variant	
Oesophageal cancer	rs1632346, rs9505309	BLOC1S5-TXNDC5: Intron Variant	(13)
	rs2815128, rs2815142	BLOC1S5: Intron Variant, BLOC1S5-TXNDC5: Intron Varian, EEF1E1-BLOC1S5: Intron Variant	
Rheumatoid arthritis(RA)	rs1225936, rs1225938, rs2743992, rs372578, rs408014	BLOC1S5-TXNDC5: Intron Variant, TXNDC5: Intron Variant	(14)
	rs2743992	BLOC1S5: Intron Variant, BLOC1S5-TXNDC5: Intron Varian, EEF1E1-BLOC1S5: Intron Variant	
	rs41302895	BLOC1S5-TXNDC5: Non Coding Transcript Variant, BMP6: 3 Prime UTR Variant, TXNDC5: 3 Prime UTR Variant	
	rs9392189	BLOC1S5: Intron Variant, BLOC1S5-TXNDC5: Intron Variant, EEF1E1-BLOC1S5: Intron Variant	
	rs9505298	BLOC1S5-TXNDC5: 500B Downstream Variant, BMP6: 3 Prime UTR Variant, TXNDC5: 500B Downstream Variant	

(Continued)

TABLE 1 Continued

Disease susceptibility	SNPs	Gene: Consequence	Ref
Ankylosing spondylitis (AS)	rs1225937, rs1225938, rs372578, rs89715, rs378963, rs1225944 rs1225947, rs1238994, rs69086, rs408014, rs368074, rs1225954 rs1225955, rs13209404	BLOC1S5-TXNDC5: Intron Variant, TXNDC5: Intron Variant	(14)
	rs1044104	BLOC1S5-TXNDC5: 500B Downstream Variant, BMP6: 3 Prime UTR Variant, TXNDC5: 500B Downstream Variant	
	rs3812162	BLOC1S5-TXNDC5: Intron Variant, TXNDC5: 2KB Upstream Variant	
Non-segmental vitiligo (NSV)	rs1043784	BLOC1S5-TXNDC5: Non Coding Transcript Variant, BMP6: 3 Prime UTR Variant, TXNDC5: 3 Prime UTR Variant	(15)
	rs7764128	BLOC1S5-TXNDC5: Non Coding Transcript Variant, TXNDC5: 3 Prime UTR Variant, BMP6: 500B Downstream Variant	
	rs8643	BLOC1S5-TXNDC5: Non Coding Transcript Variant, TXNDC5: 3 Prime UTR Variant	
Schizophrenia	rs1225934	BMP6: Intron Variant	(16)
	rs13873	BLOC1S5-TXNDC5: Intron Variant, TXNDC5: Intron Variant	

pro-inflammatory cytokine interleukin 17A (IL-17A) induces fibrosis in the lungs, liver, kidneys, heart, and skin (56–61). IL-13 selectively induces and activates TGF-β in macrophages to promote fibrosis and promotes fibrosis independently of TGF-β by directly targeting stromal and parenchymal cells (62–64). TXNDC5 plays a critical role of endoplasmic reticulum protein disulfide isomerase (PDI) activity in TGFβ- mediated tissue fibrosis. TGFβ upregulates TXNDC5 by increasing ER stress levels and activating transcription factor 6 (ATF6)-mediated transcriptional regulation. Increased TXNDC5 lead to organ fibrosis by promoting myofibroblasts activation and excessive accumulation of extracellular matrix (ECM) proteins. Highly expressed TXNDC5 contributes to cardiac fibrosis (CF) by promoting ECM protein folding (65).
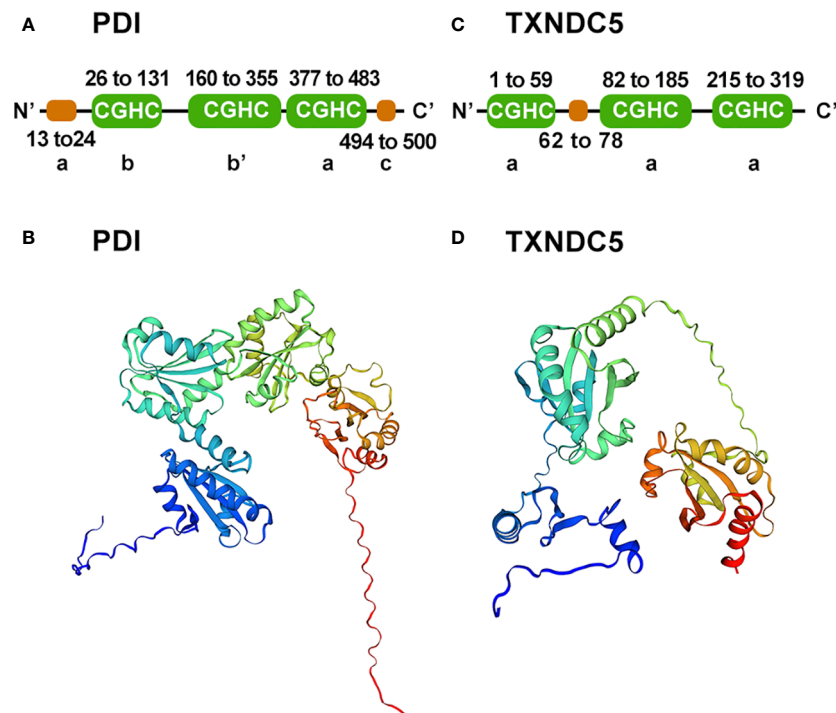
FIGURE 1
Schematic diagram of the PDI and TXNDC5 structures. **(A)** Prototypical PDI secondary structure domains were analyzed using SMART. PDI consists of four Trx-like domain (a, b, b', a') and a C-terminal domain(c). **(B)** Prototypical PDI three-tier structure was built using SWISS-MODEL. **(C)** TXNDC5 secondary structure domains were analyzed using SMART. TXNDC5 contains there Trx-like domain(a). **(D)** TXNDC5 three-tier structure was built using SWISS-MODEL.

Upregulated TXNDC5 can enhance TGFβ1 signaling by promoting the folding and stabilization of TGFBR1 in lung, leads to pulmonary fibrosis (PF) (66). TXNDC5 triggers renal fibrosis (RF) through enhancing TGF-β signaling pathway in renal fibroblasts (67). TXNDC5 promotes hepatic stellate cell activity and ECM through JNK and STAT3 signaling, thereby causing liver fibrosis (LF) (68). In conclusion, the TGFβ-ATF6-TXNDC5 signaling axis highlights the role of TXNDC5 in fiber formation during the development of fibrosis in heart, lung, kidney and liver organs (69).

TXNDC5 is involved in the tumorigenesis and progression by participating in inflammatory response. Multiple studies demonstrates that inflammation is closely relevant to the onset and progression of cancers (70–73). Specifically, chronic inflammation is involved in immunosuppression, acute inflammation induces cancer cell death via antitumor immunity, and the inflammatory response is also involved in anticancer therapies (74–76). For instance, TNF-α and IL-1β can play an important role in the occurrence of colorectal cancer through increasing the Toll-IL-1 receptor signaling (77). IL-17 produced by γδ T cells plays a key role in breast cancer metastasis (78). Additionally, TXNDC5 promotes cancer progression by regulating various inflammatory factors. TXNDC5 induces rhabdomyosarcoma proliferation survival and migration by regulating interleukin-24 (IL-24) (79), which has a wide range of anticancer activities and gradually be used in clinical therapy (80–82). TXNDC5 can also contributes to abnormal angiogenesis in cervical cancer by regulating inflammatory factor receptor expression of SERPINF1 and TRAF1, which can activate the NF-κB signaling in inflammatory environments (12, 83, 84). In conclusion, the insights have the potential to open new avenues in cancer treatment by targeting TXNDC5 to control aberrant inflammatory responses.

In conclusion, TXNDC5 directly or indirectly regulates inflammatory factors and promotes inflammatory responses (Figure 2).

4 The role of TXNDC5 in rheumatoid arthritis pathogenesis

RA is a systemic autoimmune disease characterized by the proliferation of synovial fibroblasts (SFs), which produce a variety of proteases and inflammatory factors that destroy bone and cartilage (85). In the early stages of RA, the immune system is activated and immune cells (Dendritic cells, T cells and B cells) (86, 87) infiltrate joint tissues, leading to intra-articular hyperplasia and thus inducing synovial hypoxia and hypoperfusion (88). Furthermore, hypoxia induces the overexpression of TXNDC5. Chang et al. found that the expression of TXNDC5 is high in the synovial tissue and blood of RA patients by immunohistochemistry and western blotting (13, 89). Nine SNPs located in the TXNDC5 gene (rs1225936, rs1225938, rs2743992, rs372578, rs408014, rs41302895, rs443861, rs9392189, rs9505298) were found to be closely associated with RA susceptibility (14). Subsequently, Wang et al. found that hypoxia induced TXNDC5 overexpression in the synovial tissues of RA patients, which stimulated synovial fibroblasts to produce adiponectin (ADP). ADP subsequently
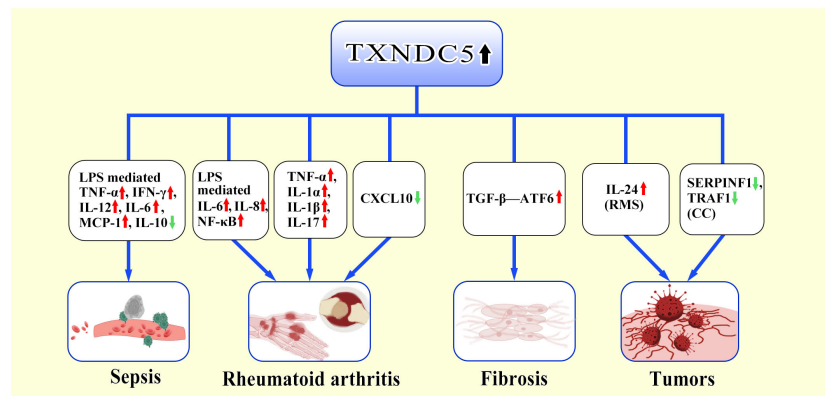
FIGURE 2
TXNDC5-mediated inflammatory response. TXNDC5 involves in multiple disease by regulating multiple inflammatory factors and inflammatory factor receptors. In sepsis, highly expressed TXNDC5 upregulates pro-inflammatory factors (TNF-α, IFN-γ, IL-12, IL-6, MCP-1) via LPS and downregulates the production of anti-inflammatory factors (IL-10). In RA, TXNDC5 exacerbates RA through LPS-mediated induction of pro-inflammatory factors (IL-6, IL-8, NF-κB); Highly expressed TXNDC5 can upregulate pro-inflammatory factors (TNF-α,IL-1α, IL-1β,IL-17) to promote RA development; Increased TXNDC5 can promote the occurrence of RA by inhibiting CXCL10. In the progress of organ fibrosis, TXNDC5 can mediate the TGFβ-ATF6-TXNDC5 signaling axis to induce multiorgan fibrosis. In tumors, TXNDC5 promotes proliferation of rhabdomyosarcoma (RMS) by inducing IL-24; TXNDC5 contributes to cervical carcinoma (CC) progression by decreasing the expression of SERPINF1 and TRAF1.

stimulated synovial fibroblasts secrete cytokines and chemokines to promote inflammation, leading to RA (90). Through further studies, Wang et al. found that increased expression of TXNDC5, toll like receptor 2 (TLR2) and epidermal growth factor receptor (EGFR) could be suppressed by enhancing miR-573 expression during TXNDC5-induced RA, thereby alleviating inflammation (53). Meanwhile, Wang et al. revealed that the expression of TXNDC5 can be upregulated in response to inflammatory factors (LPS, TNF-α and IL-6) and under the control of NF-κB signaling. They found that heat shock cognate 70 protein (HSC70) forms a complex with TXNDC5 in the cytoplasm and their directly interaction can be strengthened in the presence of LPS, TNF-α and IL-6. Further research indicated that LPS stimulation is a key point in IκBβ nuclear translocation and subsequent NF-κB activation. HSC70 activates NF-κB signaling by destabilizing IκBβ protein in the absence of LPS or promoting its nuclear translocation in the presence of LPS. In the nucleus, newly synthesized IκBβ is in a quiescent statement and the NF-κB signaling is activated. Thus, TXNDC5 plays a pro-inflammatory role in RASFs by potentiating the effects of HSC70/IκBβ-mediated NF-κB signaling (11). Thus, the TXNDC5/HSC70-mediated inflammatory pathway forms a vicious circle in the progression of RA, and the two complement each other to play an important role in the RA process. Wang et al. also found that TXNDC5 could promote RA by upregulating TNF-α, IL-1α, IL-1β, and IL-17 (90). Xu et al. found that TXNDC5 overexpression inhibited CXCL10 and tumor necrosis factor-related apoptosis-inducing ligand TNF superfamily member 10 (TRAIL) expression, further contributing to the abnormal proliferation, apoptosis and angiogenesis of RASFs (54). Li et al. asserted that TXNDC5 induces insulin resistance and increases the risk of diabetes mellitus (DM) by inhibiting the expression of insulin-like growth factor binding protein-1 (IGFBP1) (91). The onset and progression of DM are closely related to systemic inflammation and insulin resistance, which is a state of impaired glucose metabolism and insulin dysfunction (92). It was reported that most patients with RA are insulin resistant (93–97). These studies suggested that there is a close connection between RA and DM. The study conducted by Alexander et al. revealed that the levels of fasting glucose are increased in 9 individuals with loss-of-function (LOF) variation in TXNDC5, indicating TXNDC5 can be identified as a potential determinant of type 1 diabetes risk (98).

In conclusion, the above studies regarding RA revealed the important facilitating role of TXNDC5 in RA progression and provide a new therapeutic target for the future treatment of RA (Figure 3).

5 The role of TXNDC5 in the pathogenesis of organ fibrosis diseases and its underlying mechanism

A growing body of data suggests a strong link between TXNDC5 and fibrotic diseases. TXNDC5 was found to be highly expressed in multiple fibrotic diseases, and TXNDC5 is a key pathogenic factor in multiple organ fibrotic diseases. In 2018, Shih et al. used RNA sequencing and gene co-expression network analysis to analyze data from failing human hearts, and found that TXNDC5 was highly upregulated in failing human left ventricular (LVs) (65). Highly expressed TXNDC5 can promote ECM enrichment to induce myocardial fibrosis by increasing NOX4-derived ROS and activating redox-sensitive JNK signaling. CF can lead to cardiac structural and functional remodeling, triggering diastolic dysfunction (99, 100) and consequently heart failure (HF). Increased levels of TXNDC5 expression further enhance the excessive accumulation of myofibroblasts and ECM proteins, leading to CF (65). Suppress the expression of TXNDC5 therefore
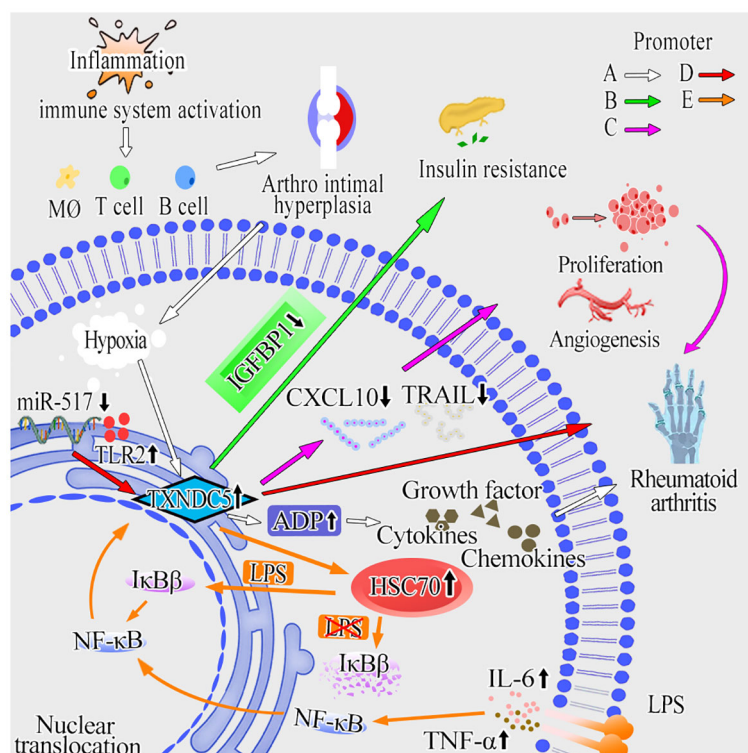
FIGURE 3

The molecular mechanisms of TXNDC5 promotes RA. **(A)** Inflammation can activate the body's immune system and contribute to hyperplasia of the joint lining. Hypoxia and hypoperfusion are induced by arthro intimal hyperplasia and increase TXNDC5 expression subsequently. By upregulating ADP, TXNDC5 secretes cytokines, chemokines and growth factors to promote inflammation and RA progression (white arrow). **(B)** TXNDC5 lead to insulin resistance and increase the risk of developing diabetes mellitus by inhibiting the expression of IGFBP1 (green arrow). **(C)** TXNDC5 can inhibit the expression of CXCL10 and TRAIL, leading to abnormal proliferation, apoptosis, and angiogenesis in RASFs (pink arrow). **(D)** Inhibit the expression of miR-573 in RA increased the expression of TXNDC5 and TLR2, which then exacerbates inflammation and induces RA (red arrow). **(E)** The expression of TXNDC5 can be upregulated in response to inflammatory factors (LPS, TNF-α and IL-6) and under the control of NF-κB signaling. In the absence of LPS, HSC70 forms a complex with TXNDC5 in the cytoplasm, and then activates NF-κB signaling by destabilizing IκBβ protein to induce RA; In the presence of LPS, IκBβ can translocate into the nucleus and facilitate the activity of p65, promoting transcription of TXNDC5 and RA progression (orange arrow).

provides a new therapeutic target for the treatment of CF, in contrast to traditional therapeutic modalities, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonist (MRA) (101–103). Targeting TXNDC5 does not limit the slowing of CF due to lower blood pressure. Moreover, inhibiting TXNDC5 expression can limit CF progression by silencing TGF-β1, thus attenuating fibroblast activation, ECM enrichment (65, 104, 105) and evading hepatotoxicity (106). In summary, silencing TXNDC5 provides new therapeutic strategies to alleviate CF and prevent HF.

In 2020, Lee et al. found that TXNDC5 was highly upregulated in lung tissue from patients with idiopathic pulmonary fibrosis and a bleomycin (BLM)-induced PF mouse models (66). TGF-β and TGFBR2 binding activates the TGFBR1/ER stress/ATF6 transcriptional pathway to drive TXNDC5 enrichment in lung fibroblasts, which in turn induces fibroblast hyperactivation, proliferation, and ECM enrichment through activation of TGF-β classical (SMAD3) (107) and nonclassical (JNK, ERK, PI3K, p38, MAPK) signaling (108), leading to PF. Suppress the TGF-β pathway represents an attractive approach to treat pulmonary fibrosis, but

extensive inhibition of TGF-β leads to hepatotoxicity (109) and cardiotoxicity (110, 111); targeting knockdown of TGF-β1 causes interstitial pneumonia and systemic perivascular inflammation (112, 113); and targeting inhibition of TGFBR1 promotes impaired alveolar and epithelial cell production (114). TGF-β expression is necessary for lung organogenesis and homeostasis *in vivo* (115), therefore, direct down regulation of TGF-β rarely reaches the early clinical trial stage (109). However, compared with TGF-β, inhibit the expression of TXNDC5 showed no significant adverse effects.

Chen et al. Microarray data from renal biopsy specimens from CKD patients were analyzed and increased renal TXNDC5 expression was verified using gene knockout, flow cytometry, and immunohistochemistry. This study experimentally hypothesized to be under the control of the TGF-β1/ATF6/TXNDC5/TGFBR1 signaling axis, resulting in the enhancement of the folding and stability of TGFBR1. The signaling pathway leads to the amplification of TGF-β1 signaling and a series of renal fibrotic responses (67). Studies have shown that inflammation, tubular injury and other factors increase pro-fibrotic and inflammatory factors, inflammatory cells in large amounts, including TGF-β and

macrophages (116). TGF-β is a key factor in the development of RF (117). Increasing expression of TGF-β drives fibroblast activation into collagen-secreting myofibroblasts (118–120), characterized by α-smooth muscle actin (αSMA) expression and excessive ECM deposition, leading to abnormal renal structure (121). In the process of treating RF, Chen et al. found that TXNDC5 deletion effectively ameliorated the development and progression of RF induced by various injuries in mice (67), providing a new and effective method for treating RF.

Hung et al. studied liver fibrosis (LF) and validated that the TGFβ/ATF6/TXNDC5/JNK/STAT3 signaling axis, suggesting that TXNDC5 plays a key role in the formation of LF (68). LF is generally caused by chronic liver injury (122), such as viral infections, nonalcoholic steatohepatitis (NASH), alcohol consumption (AC) and biliary obstructive disease (123, 124). Chronic hepatocellular injury could lead to epithelial/endothelial barrier damage, the release of inflammatory cytokines and the agglomeration of inflammatory cells followed by the secretion of profibrotic cytokines. Hepatic stellate cells (HSC) are activated and transformed into myofibroblasts, which leading to ECM enrichment, fibrous septa formation and regenerative nodules (124, 125). The activation of hepatic stellate cells into myofibroblast-like cells is the central link in the development of LF (126). Therefore, therapies that reduce HSC activation and ECM accumulation have become the mainstay of treatment for LF. TXNDC5 activates HSC through reactive oxygen species (ROS)-dependent JNK signaling; TXNDC5 also enables HSCs to avoid apoptosis via STAT3 signaling, leading to the enrichment of activated HSCs and excessive fibrotic in the liver. Inhibition of the catalytic function of TXNDC5 abrogates JNK and STAT3 activation, leading to downstream fibrotic responses (68). Silencing TXNDC5 reduces liver fibrosis in mice (127). Targeting TXNDC5 in HSCs reduces LF through limiting HSC cell activation by inhibition of noncanonical TGF-β signaling.

In summary, TXNDC5 is associated with key factors that promote the development of organ fibrosis. Targeting TXNDC5 deletion may be a potential new therapeutic strategy to improve fibrotic disease (Figure 4, Table 2).

6 TXNDC5 and tumor tissues

6.1 TXNDC5 is highly expressed in a variety of tumor tissues

Increasing evidence has revealed that TXNDC5 and tumors progression are closely related (128). Several studies found that TXNDC5 showed significantly increased expression in a variety of cancer tissues. Chang et al. found that TXNDC5 was significantly expressed in tumor tissues, including invasive ductal carcinoma of the breast, squamous cell carcinoma of the cervix, squamous cell carcinoma of the esophagus, papillary plasmacytoma of the ovary, and prostate cancer (13). It was reported that TXNDC5 was also found to have procarcinogenic effects in tissues of several cancers, including prostate cancer (PCa) (129), colorectal cancer (CRC) (130) (127), lung cancer (LCA) (131), non-small cell lung cancer (NSCLC) (132), ovarian cancer (OC), gastric cancer (GC) (133, 134), cervical cancer

(CC) (12), esophageal squamous cell carcinoma (ESCC) (135), and hepatocellular carcinoma (HCC) (136). In samples from patients with LCA, TXNDC5 protein expression was upregulated in more than 60% of NSCLC tissues (137). Batool et al. found that the increased expression of TXNDC5 was mostly due to increased levels of transcription and translation of the *TXNDC5*, especially the increased transcription of the *TXNDC5*, which was also found in tissues obtained from patients in the early stages of colorectal cancer (130). In addition, several experiments have demonstrated that TXNDC5 is overexpressed in colorectal cancer tissues, revealing that TXNDC5 is a tumor-enhancing gene that promotes the proliferation and migration of a variety of tumor cells. By immunohistochemical studies, Wu et al. found that TXNDC5 was highly expressed in gastric cancer cells, particularly in hypofractionated adenocarcinoma (133). Regarding hepatocellular carcinoma tissue, TXNDC5 expression is increased in poorly differentiated hepatocellular carcinomas but not in highly differentiated tumors. In Pca, TXNDC5 was significantly overexpressed in androgen-intrinsic prostate cancer and desmoplastic-resistant prostate cancer (129). In ESCC, Wang et al. found that TXNDC5 showed highly expression, indicating that ESCC with high TXNDC5 expression had a poor prognosis (135). By using in silico analysis, Kocatürk et al. found that the expression pattern of TXNDC5 family members is different between tumor tissues and healthy tissues, and the expression of TXNDC5 is proportional to the grades of diffuse glioma tumors (138). In summary, TXNDC5 is a typical cancer-enhancing gene that is highly expressed and overexpressed in tumor tissues of several cancers and plays an important role in the development of cancer.

6.2 The regulatory mechanism of TXNDC5 in cancer development

6.2.1 Hypoxia induces high expression of TXNDC5

TXNDC5, like most members of the PDI family, is involved in the correct folding and formation of disulfide bonds in newly synthesized proteins through disulfide isomerase and chaperone protein activity, and plays an important role in prevention of endoplasmic reticulum stress (5–7). Sullivan et al. found that PDI was needed for endothelial cell survival under both normoxic and hypoxic conditions, but TXNDC5 was only highly expressed and exerted a protective effect on endothelial cells under hypoxic conditions. Tan et al. found that hypoxia could induce upregulation of TXNDC5 in colorectal cancer tissues by elevating the expression of hypoxia-inducible factor-1α (HIF-1α), leading to reduced ROS production (130). It was previously reported that ROS is directly or indirectly involved in endoplasmic reticulum homeostasis and protein folding, thereby triggering endoplasmic reticulum stress and possibly inducing apoptosis in response to excessive endoplasmic reticulum stress (139). Hypoxia can inhibit hypoxia-induced ROS/ER stress signaling and promote proliferation and clone formation in colorectal cancer cells by inducing TXNDC5 overexpression through the upregulation of HIF-1α (130). Wang et al. observed that TXNDC5 was upregulated in prostate cancer cells after prolonged androgen deprivation therapy (ADT) due to ADT-induced hypoxia upregulating TXNDC5
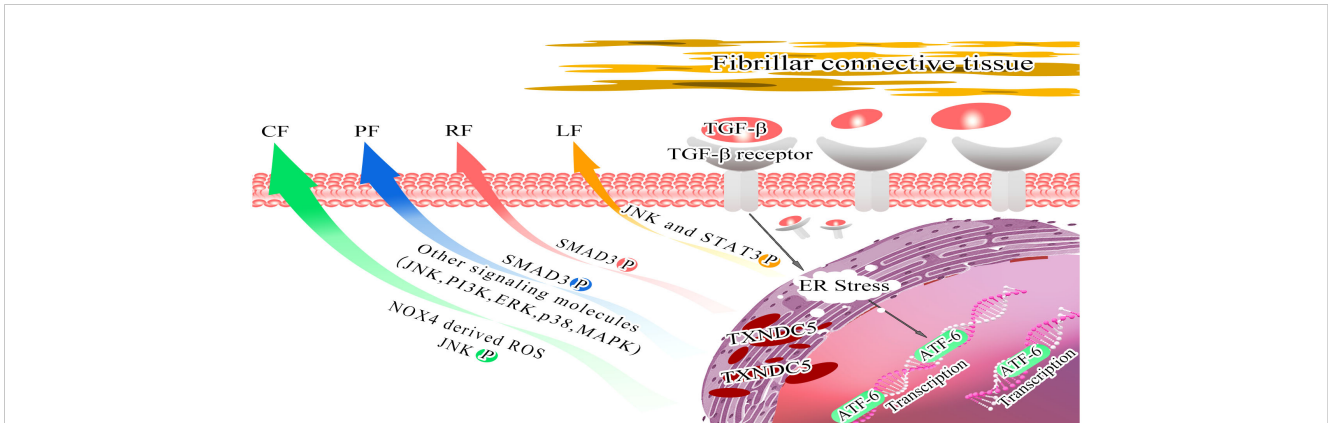
FIGURE 4
Model depicting the role of TXNDC5 promote multiorgan fibrosis. Stimulation of endoplasmic reticulum stress by TGFβ activates ATF6-mediated transcriptional branching, contributing to the upregulation of TXNDC5 expression, which mediates downstream effector molecules to induce organ fibrosis. Increased TXNDC5 expression induces CF by increasing NOX4-derived ROS and activating redox-sensitive JNK signaling (green arrow); leads to PF by activating SMAD3 phosphorylation and inducing other signaling molecules (JNK, PI3K, ERK, p38 and MAPK) (blue arrow); leads to RF by activating SMAD3 signaling (red arrow); and leads to LF by activating JNK signaling and STAT3 signaling (orange arrow).

expression through androgen receptor (AR) protein signaling, thereby enhancing their interaction, stability and transcriptional activity. This mechanism further regulates TXNDC5 expression through HIF-1α and miR-200b-dependent pathways (129). The above results suggest that TXNDC5 may play a role as a hypoxia-induced stress survival factor in tumor cells, contributing to tumor cell growth and proliferation under hypoxic conditions.

6.2.2 The diverse oncogenic mechanism of TXNDC5 in various cancers

Numerous studies have shown that increased TXNDC5 expression is regulated by multiple factors. In 2017, Xu et al. demonstrated that TXNDC5 is a susceptibility gene in cervical cancer using Taqman genotype. They point out that TXNDC5 is highly expressed in cervical squamous cancer tissues. TXNDC5 can promote angiogenesis, angiogenic mimicry and cell metastasis in cervical cancer (12). Du et al. identified TXNDC5 as a target of MELLT3 mediated m6A modification by MeRIP-seq, and

confirmed the positive correlation between TXNDC5 and METTL3 at the protein and RNA levels. Their further study found that the m6A readers (YTHDF2 and IGF2BP2/3) could interact with TXNDC5 mRNA. Mechanically, IGF2BP2/3 enhanced TXNDC5 mRNA stability, whereas YTHDF2 may promote TXNDC5 mRNA degradation. Thus, METTL3 promotes proliferation and metastasis of CC cells by upregulating TXNDC5 expression via m6A-reader-dependent way (140). Yu et al. demonstrated that circRNA-104718 acts as a competitive endogenous RNA for miR-218-5p to regulate TXNDC5 in HCC, and thus promote HCC (141). The next year, Zang et al. detected significantly elevated protein levels of TXNDC5 in HCC tissues and cells by western blotting, and found that circ_0000517 could promote TXNDC5 overexpression by inhibiting miR-1296-5p. Further research shown that TXNDC5 overexpression could enhance HCC cell viability, promote HCC cell colony formation, shorten cell cycle, and promote cell proliferation and migration (136). Wang et al. confirmed that HERG1 induces to poor prognosis

TABLE 2 TXNDC5 promotes the organ fibrosis signaling pathway.

Organ Fibrosis	Disease Abbreviation	TXNDC5 Upstream adjustment pathway	Downstream effectors	Results	Reference
Cardiac fibrosis	CF	TGFβ/ER stress/ATF6 mediates transcription	1.NOX4-derived ROS 2. Phosphorylated JNK signaling	Fibroblast activation and excessive accumulation of ECM proteins contribute to CF	(65)
Pulmonary fibrosis	PF	TGFβ binding to TGFBR2 activates TGFBR1/ER stress/ATF6-mediated transcription	1. SMAD signal 2. Other signaling molecules (JNK, ERK, PI3K, p38, MAPK)	Fibroblast activation and excessive accumulation of ECM proteins contribute to PE	(66)
Renal fibrosis	RF	TGFβ binding to TGFBR2 activates TGFBR1/ER stress/ATF6-mediated transcription	1. Redox-sensitive SMAD3 signaling	Fibroblast activation and excessive accumulation of ECM proteins contribute to RF	(67)
Liver Fibrosis	LF	TGFβ/ER stress/ATF6 mediates transcription	1. Redox-sensitive JNK signaling and STAT3 signaling	Fibroblast activation and excessive accumulation of ECM proteins contribute to LF	(68)

in esophageal squamous cell carcinoma (ESCC) patients by promoting cell proliferation, migration, and invasion, while these effects can be reversed by altering the expression of TXNDC5 and its downstream PI3K/AKT pathway. The study suggested that TXNDC5 is a key point in the pathway of HERG1 promotes tumor progression (135). Ge et al. revealed that the TBX15/TXNDC5 axis play a crucial role in the genesis and progression of glioma; TBX15 exerts its oncogenic roles by regulating transcriptional activation of TXDNC5 (142). Overall, these results indicate that TXNDC5 is affected by different regulators in various cancers and that TXNDC5 plays an important role in promoting cancer proliferation, invasion and metastasis.

TXNDC5 also influenced by other factors that promote the development of cancer. For example, TXNDC5 expression is induced by three endoplasmic reticulum stress conditions, including glucose deprivation, serum deprivation and the presence of tunicamycin (TM) (143, 144), endoplasmic reticulum stress is a key factor in tumor-promoting mechanisms (144), which affect protein glycosylation and ATP production, leading to endoplasmic reticulum stress and the accumulation of unfolded or misfolded proteins. In clear cell renal cell carcinoma (ccRCC), ccRCC cells adapt to this stressful environment and escape apoptosis (143). In pancreatic cancer, NR4A1 (Nur77, TR3) regulates TXNDC5 expression, maintains low levels of stress by ROS in cancer cells, and promotes pancreatic cancer cell proliferation (145). Chawsheen et al. demonstrated that TXNDC5 interacts with sulfiredoxin (Srx) through IP experiments and that the two together maintain endoplasmic reticulum homeostasis in human lung cancer cells, thereby promoting cell colony formation and migration (131). Charlton et al. found that TXNDC5 inhibited the lipocalin signal pathway by interacting with AdipoR1 in HeLa cells (9). Regarding to renal cell carcinoma (RCC), the ratio of TXNDC5/AdipoR1 expression was significantly higher in metastatic renal cell carcinoma tissues than in nonmetastatic controls (146). The presence of TXNDC5 in metastatic renal cell carcinoma promotes cell growth, migration, invasion and increases resistance of cancer cells to chemotherapeutic agents (143). However, there is not sufficient evidence for a stable interaction between AdipoR1 and TXNDC5 (146). Moreover, it is possible that the interaction between AdipoR1 and TXNDC5 is regulated by various interaction factors and therefore varies due to the characteristics of the interaction factors. It is debatable whether the tumorigenic properties of TXNDC5 expression in RCC cells are related to the inhibitory regulation of lipocalin tumor suppressor signaling.

In summary, TXNDC5 has different oncogenic mechanisms in different cancers, and the complex mechanisms of TXNDC5 in cancer tissues deserve further exploration (Figure 5).

6.3 TXNDC5: a promising potential tumor diagnostic marker or therapeutic target

TXNDC5 can be used as a diagnostic marker and a therapeutic target in cancer. Decrease the expression of TXNDC5 in cancer tissues can attenuate cell viability, inhibit cell colony formation,

induce cell cycle arrest and apoptosis. In ccRCC, TXNDC5 can be used as a prognostic criterion for patients (143). Ren et al. also found that the expression of TXNDC5 was negatively correlated with the chemosensitivity of ccRCC, and inhibit the expression of TXNDC5 increased the resistance of ccRCC to chemotherapeutic drugs, reduced the killing of cancer cells by chemotherapeutic drugs, and promoted the development of cancer (143). These results indicated that TXNDC5 probably can be used as a diagnostic and prognostic biomarker, indicating that TXNDC5 is a promising therapeutic target for ccRCC. In gastric adenocarcinoma tissues Wu et al. found that TXNDC5 is highly expressed in gastric cancer cells by immunohistochemistry and its expression is significantly increased in poorly differentiated adenocarcinomas, suggesting that the expression of TXNDC5 is significantly associated with the prognosis of gastric adenocarcinomas at the cardia (133). Nissom et al. identified that TXNDC5 was expressed in HCC but not in highly differentiated HCC, indicated that the expression of TXNDC5 could be used to predict the progression of HCC. In CRC (130) and NSCLC (137), TXNDC5 is highly expressed in the early stages of cancer, so TXNDC5 can be used as a means to diagnose early cancer. Chawsheen et al. revealed that inhibiting the expression of TXNDC5 may reduce the incidence of lung cancer. Further research indicated that the Srx-TXNDC5 complex may be used to predict the survival probability for lung cancer patients and as a therapeutic target or molecular diagnostic tool in human lung cancer pathogenesis (147). In brief, TXNDC5 is a promising prognostic marker for cancer progression, a therapeutic target and a molecular diagnostic indicator for cancer pathogenesis. In conclusion, TXNDC5 plays an essential role in cancer diagnosis and therapy.

7 The role of TXNDC5 in other diseases

It is well known that TXNDC5 is regulated by hypoxia (3), which induces vasoconstriction and coronary arteriosclerosis. Camargo et al. reported that TXNDC5 promotes the expression of proangiogenic proteases by regulating AP-1-dependent gene expression and induces angiogenesis in response to TNF-α (8). Yeh et al. revealed that TXNDC5 promotes atherosclerosis *in vivo*. Mechanically, TXNDC5 induces ubiquitination and proteasome-mediated degradation of HSF1, destabilizes eNOS protein by inhibiting HSP90 (148). Their further studies found that TXNDC5 deletion in vascular endothelium result in increased eNOS protein and reduced atherosclerosis in apoE$^{-/-}$ mice. Meanwhile, Kuhlencordt et al. found that atherosclerosis, aortic aneurysm formation and ischemic heart disease are accelerated in apoE/eNOS double knockout mice (149). These above findings indicates that TXNDC5 may lead to vascular diseases through regulating apoE and eNOS.

Holmgren et al. recently found that loss-of-function mutations in TXNDC5 may prevent key peptides from functioning properly, thus causing insulin hypersecretion (150). This resulted in insufficient insulin secretion. Subsequently, Alexander et al. showed that TXNDC5 could catalyze the reduction of insulin disulfide bonds and weaken the binding activity of insulin to the insulin receptor, thus causing abnormalities in glucose tolerance in
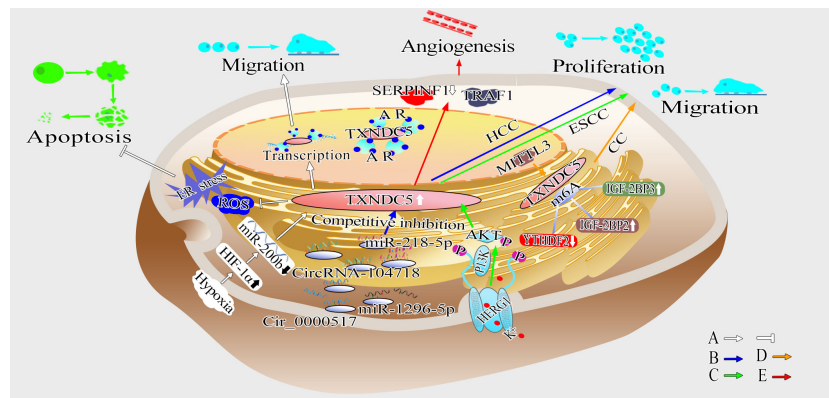
FIGURE 5
Schematic diagram showing the mechanism by which TXNDC5 promotes cancer. **(A)** TXNDC5 can be upregulated under hypoxia and play a crucial role in anti-apoptosis by regulating hypoxia-induced ROS/ER stress signaling; Hypoxia induce the expression of TXNDC5 through HIF-1α in an miR-200b-dependent manner, and strengthen the interaction between TXNDC5 and AR to promote proliferation and migration (white arrow). **(B)** Circ_0000517 and circRNA-104718 acted as miR-1296-5p and miR-218-5p competitive endogenous RNAs, respectively, upregulating TXNDC5 expression to promote HCC proliferation and metastasis (blue arrow). **(C)** HERG1 leads to ESCC proliferation, migration and invasion through TXNDC5 by mediating the PI3K/AKT signaling pathway (green arrow). **(D)** METTL3 promotes proliferation and metastasis of cervical cancer (CC) cells by upregulating TXNDC5 expression via m6A-reader-dependent way (orange arrow). **(E)** Highly expressed TXNDC5 can promote angiogenesis by inhibiting the expression of SERPINF1 and TRAF1 (red arrow).

the body, revealing an important role for TXNDC5 in promoting the development of diabetes (98). Recently, Li et al. found that high expression of TXNDC5 inhibited the expression of IGFBP1 to induce insulin resistance, increasing the risk of developing DM (91).

Ramírez et al. found that the severity of fatty liver induced by apolipoprotein E (ApoE) knockout was negatively correlated with the levels of TXNDC5 protein and mRNA. Their further study revealed that the expression of TXNDC5 reflected squalene's anti-lipotropic properties and sensitivity to lipid accumulation (151). Karatas et al. found that four members of the PDI family (TXNDC5, PDIA4, PDIA3 and P4HB) were specifically upregulated in adult ZZ-AATD-mediated liver disease by studying hepatocyte function in patients with ZZ-type α1-antitrypsin deficiency (152). In the mechanism of interferon-stimulated gene 15 (ISG15)-induced hepatitis C virus (HCV) infection, ISG15 may promote HCV replication by regulating TXNDC5 (153–155).

Kim et al. found a correlation between TXNDC5 and skin aging by immunohistochemical assay and qRT–PCR in the skin tissues of 20 patients (156). In addition, TXNDC5 expression was higher in peripheral blood mononuclear cells in young adults than in older adults, suggesting that altered TXNDC5 expression may be associated with endothelial cell apoptosis (157).

In addition, certain SNP loci of TXNDC5 are closely associated with disease susceptibility. In a Korean population, three exonic SNPs (rs1043784, rs7764128 and rs8643) in TXNDC5 were found to be positively associated with nonsegmental vitiligo (NSV) (15). A SNP (rs13873) in the TXNDC5 gene and haplotype rs1225934-rs13873 in BMP6-TXNDC5 play a role in the selective impairment of persistent attention disorder in schizophrenia (16). The TXNDC5-related SNP (rs13196892: TXNDC5 | MUTED) that may be associated with human age was first identified in a study exploring female menopause/age-related factors (158).

In addition, TXNDC5 may be a predictive marker for histone deacetylase inhibitor (HDACI) resistance in cutaneous T-cell

lymphoma during drug treatment of the disease (159), a predictive marker for resistance to bortezomib in refractory/relapsed multiple myeloma (160), a regulatory target of simvastatin to enhance docetaxel-induced cytotoxicity in human prostate cancer cells (161) and may be a key factor in the antioxidant effect of statins. Atorvastatin inhibits ROS production and Nox2 activity by promoting the membrane translocation of TXNDC5 in lipid rafts and enhancing the colocalization of TXNDC5 and Nox2, thus exerting antioxidant effects (162). Moreover, direct B lymphocyte LS-TA of TXNDC5 is an early biomarker of vaccine response in novel coronavirus pneumonia (COVID-19) (163).

In summary, TXNDC5 is expected to serve as a target for gene or drug therapy in an effort to change the trajectories of the aforementioned diseases.

8 Summary

TXNDC5, a member of the PDI protein family, is mainly found in tissues such as the brain, spleen, lung, liver, kidney, pancreas and testis. TXNDC5 consists of three redox-like Trx structural domains, each of them contains a CGHC motif that acts as an active catalytic structural domain for PDI activity, thereby regulating the rate of disulfide bond formation, isomerization and degradation of target proteins, thus altering the protein conformation and activity to improve protein stability. High expression of TXNDC5 is a key factor in the development of inflammation, cancer, rheumatoid arthritis, organ fibrosis, diabetes and other diseases.

In sepsis, RA and many other inflammatory diseases, TXNDC5 mediates the expression of a variety of inflammatory factors and receptors, which promotes the inflammatory response that leads to disease.

In fibrotic diseases, TXNDC5 acts as a mediator of TGF-ß signaling and amplifies TGF-ß induced fibrotic responses through

its PDI activity to induce fibroblast activation, proliferation, and ECM production, inducing fibrosis in multiple organs such as the heart, lungs, kidneys, and liver.

In cancer, the SNPs in TXNDC5 gene are significantly associated with genetic susceptibility to a variety of cancers, including cervical cancer, hepatocellular carcinoma, liver cancer and esophageal cancer. Increased TXNDC5 expression can mediate neovascularization and promote cancer cell proliferation, invasion and metastasis.

In addition, TXNDC5 is strongly associated with a variety of diseases, such as diabetes, fatty liver, schizophrenia, and NSV.

Therefore, targeting TXNDC5 provides a powerful new tool for disease diagnosis and treatment. However, the specific roles and mechanisms of TXNDC5 in different diseases are not yet fully understood, and large-scale clinical trials are needed to validate the mechanism of TXNDC5 in different diseases as well as targeted therapies in the future.

Author contributions

MJ: Writing – original draft. YZ: Writing – review & editing. XS: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. BX: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

AC	alcohol consumption
ACEI	angiotensin-converting enzyme inhibitors
ADP	adiponectin
ADT	androgen deprivation therapy
ApoE	apolipoprotein E
AR	androgen receptor
ARBs	angiotensin receptor blockers
ATF6	activating transcription factor 6
CC	cervical cancer
ccRCC	clear cell renal cell carcinoma
CF	cardiac fibrosis
CRC	colorectal cancer
CXCL10	C-X-C motif chemokine ligand 10
DM	diabetes mellitus
ECM	extracellular matrix
EDEM3	alpha -mannosidase–like protein 3
EGFR	epidermal growth factor receptor
Endo-PD	endothelial protein-disulfide isomerase
Ero1α	endoplasmic reticulum oxidoreductase1α
ESCC	esophageal squamous cell carcinoma
G-CSF	granulocyte colony-stimulating factor
GC	gastric cancer
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HF	heart failure
HDACI	histone deacetylase inhibitor
HERG1	human ether a-go-go-related gene 1
HIF-1α	hypoxia-inducible factor-1α
HSC	Hepatic stellate cells
HSC70	heat shock cognate 70 protein
HSF1	heat shock factor 1
HSPs	heat shock proteins
IGFBP1	insulin-like growth factor binding protein-1
IL-17A	interleukin 17A
Inos	induction of nitric oxide synthase
ISG15	interferon-stimulated gene 15
LCA	lung cancer
LF	liver fibrosis

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LOF	loss-of-function
LPS	lipopolysaccharide
LVs	left ventricular
MRA	mineralocorticoid receptor antagonist
NSCLC	non-small cell lung cancer
NSV	nonsegmental vitiligo
OC	ovarian cancer
PCa	prostate cancer
PDI	protein disulfide isomerase
PF	pulmonary fibrosis
prx4	peroxisomal protein 4
RA	rheumatoid arthritis
RCC	renal cell carcinoma
RF	renal fibrosis
SFs	synovial fibroblasts
Srx	sulfiredoxin
TLR2	toll like receptor 2
TM	tunicamycin
TRAIL	TNF superfamily member 10
TNF-α	tumor necrosis factor-α
TXNDC5	Thioredoxin domain containing protein-5.