TXNDC5 as a Dual-Bridge Driver of Oncogenesis: Coupling Intracellular Pro-Tumorigenic Signaling with Extracellular Fibrotic Remodeling and Cold Tumor Formation

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Abstract

Thioredoxin domain-containing protein 5 (TXNDC5), a member of the protein disulfide isomerase (PDI) family, has emerged as a critical mediator in tumor biology with dual functionality. Beyond its established role in protein folding within the endoplasmic reticulum, TXNDC5 exhibits both cell-autonomous pro-tumorigenic effects and non-cell-autonomous microenvironment remodeling capabilities. Herein, we propose the “Dual-Bridge” paradigm to conceptualize TXNDC5’s oncogenic functions: an intracellular bridge that directly promotes tumor cell proliferation, survival, and stress resistance, and an extracellular bridge wherein CAF-derived TXNDC5 drives fibrotic remodeling, vascular compression, hypoxia, and immune exclusion, culminating in cold tumor formation. This framework positions TXNDC5 as a unique molecular hub that coordinates cancer cell-intrinsic malignancy with microenvironmental immunosuppression. This review systematically integrates recent advances in understanding TXNDC5-mediated tumor microenvironment (TME) remodeling, with particular emphasis on its pivotal role in cancer-associated fibroblast (CAF) activation and the subsequent cascade leading to cold tumor formation and immunotherapy resistance. We delineate the molecular architecture of TXNDC5, its expression regulation through epigenetic modifications including m6A RNA methylation, and its divergent functions in tumor cells versus stromal fibroblasts. Central to our discussion is the "TXNDC5-TGFBR1-TGFβ" signaling axis, whereby TXNDC5 stabilizes TGFBR1 through PDI activity, amplifying TGFβ signaling in CAFs and driving extracellular matrix (ECM) deposition, tumor desmoplasia, vascular compression, and intratumoral hypoxia. This fibrotic cascade culminates in immune exclusion characterized by diminished CD8+ cytotoxic T lymphocyte infiltration, myeloid-derived suppressor cell (MDSC) accumulation, and resistance to immune checkpoint inhibitors (ICIs). We further discuss therapeutic implications,

including the potential of TXNDC5-targeted strategies to reverse immunotherapy resistance and enhance drug delivery. This comprehensive framework positions TXNDC5 as a promising target for overcoming the physical and immunological barriers that limit current cancer therapeutics. The Dual-Bridge framework not only unifies the disparate observations of TXNDC5 biology but also provides a mechanistic roadmap for targeting both bridges to reverse immunotherapy resistance.

Keywords: TXNDC5; tumor microenvironment; cancer-associated fibroblasts; desmoplasia; cold tumor; immune checkpoint inhibitor resistance; TGFβ signaling; Dual-Bridge paradigm

1. Introduction

Thioredoxin domain-containing protein 5 (TXNDC5), also known as endoplasmic reticulum protein 46 (ERp46), is encoded by the TXNDC5 gene located on chromosome 6p24.3[1]. As a distinguished member of the protein disulfide isomerase (PDI) family, TXNDC5 possesses three thioredoxin-like domains, each harboring the characteristic CGHC catalytic motif that confers oxidoreductase and isomerase activities essential for catalyzing disulfide bond formation and rearrangement during nascent polypeptide folding[1,2]. The protein contains a C-terminal KDEL sequence that ensures its retention within the endoplasmic reticulum, where it functions as a molecular chaperone facilitating proper protein folding and maintaining proteostasis under physiological conditions[3].

TXNDC5 exhibits a tissue-specific expression pattern with notably high expression in endothelial cells, fibroblasts, and pancreatic β-cells. Importantly, its expression is significantly upregulated under hypoxic conditions, a common feature of the tumor microenvironment[3,4].This hypoxia-inducible expression pattern positions TXNDC5 as a critical adaptive factor in pathological contexts characterized by oxygen deprivation and metabolic stress[4]. The conservation of TXNDC5 sequence and function across mammalian species, with approximately 95% identity between mouse and human orthologs, has facilitated the development of robust preclinical models for studying its role in cancer biology[5].

Historically regarded as a housekeeping protein involved in routine protein quality control, TXNDC5 has gained increasing recognition as a disease-critical factor[4]. Its dysregulated expression has been implicated in various inflammatory conditions, most notably rheumatoid arthritis, where it contributes to synovial fibroblast activation and joint destruction[3,6]. Furthermore, TXNDC5 has been established as a key mediator in multi-organ fibrosis, including cardiac, pulmonary, renal, and hepatic fibrosis, through its ability to stabilize TGFBR1 and amplify TGFβ signaling pathways[2,7]. These findings have provided the conceptual foundation for understanding its analogous role in tumor stromal remodeling[5,8].

Despite accumulating evidence for TXNDC5's involvement in cancer biology, existing reviews have not systematically integrated the "fibrosis-cold tumor" axis into a coherent mechanistic framework[1,4]. This review addresses this gap by presenting a comprehensive analysis that traverses from TXNDC5's molecular structure and biochemical functions to its cell-autonomous oncogenic roles, its non-cell-autonomous microenvironment remodeling activities through CAF activation, and ultimately its contribution to cold tumor formation and therapeutic resistance[5,8]. To address this gap, we introduce the “Dual-Bridge” conceptual framework—a novel paradigm that systematically integrates TXNDC5’s cell-autonomous oncogenic functions (the intracellular bridge) with its non-cell-autonomous microenvironment remodeling activities through CAF activation (the extracellular bridge) into a unified mechanistic model. This framework transcends traditional single-compartment analyses by positioning TXNDC5 as a molecular hub that simultaneously drives tumor cell proliferation and fibrotic-immune suppression, offering a comprehensive explanation for the cold tumor phenotype and therapeutic resistance. We propose that targeting CAF-derived TXNDC5 represents a novel strategy to reverse immunotherapy resistance and enhance the efficacy of existing cancer treatments[5]. The Dual-Bridge framework provides three key advances: (1) it unifies the previously disparate observations of TXNDC5’s cell-intrinsic and stroma-remodeling functions; (2) it establishes a causal link from CAF-specific TXNDC5 upregulation to cold tumor formation through the fibrotic-hypoxic-immunosuppressive cascade; and (3) it offers a mechanistic rationale for targeting both bridges to overcome immunotherapy resistance.

2. Molecular Basis and Functional Diversity of TXNDC5

2.1 Structural and Biochemical Functions

The three thioredoxin domains of TXNDC5 function cooperatively to facilitate oxidative protein folding. Each domain's CGHC motif cycles between oxidized and reduced states, enabling the catalysis of disulfide bond formation, reduction, and isomerization[9]. This enzymatic versatility allows TXNDC5 to process a broad spectrum of substrates, including secreted proteins, membrane receptors, and extracellular matrix components. The specificity of TXNDC5 for particular substrates appears to be dictated by the unique cysteine pattern and secondary structure of target proteins, distinguishing it from general antioxidant proteins[10]. TXNDC5 also collaborates with other chaperone proteins, such as heat shock cognate 70 kDa protein (HSC70), to ensure efficient folding and prevent protein aggregation under conditions of endoplasmic reticulum stress[11]. This chaperone network is particularly relevant in the tumor context, where rapid proliferation and hypoxia create sustained proteostatic stress[12]. The structural organization of TXNDC5 and its chaperone-mediated stabilization of TGFBR1 are schematically depicted in Figure 1. Panel A illustrates the three-domain architecture with CGHC catalytic motifs, Panel B demonstrates the PDI-dependent prevention of TGFBR1 misfolding and

ubiquitination, and Panel C shows the resulting feed-forward amplification of TGFβ signaling in CAFs[13].

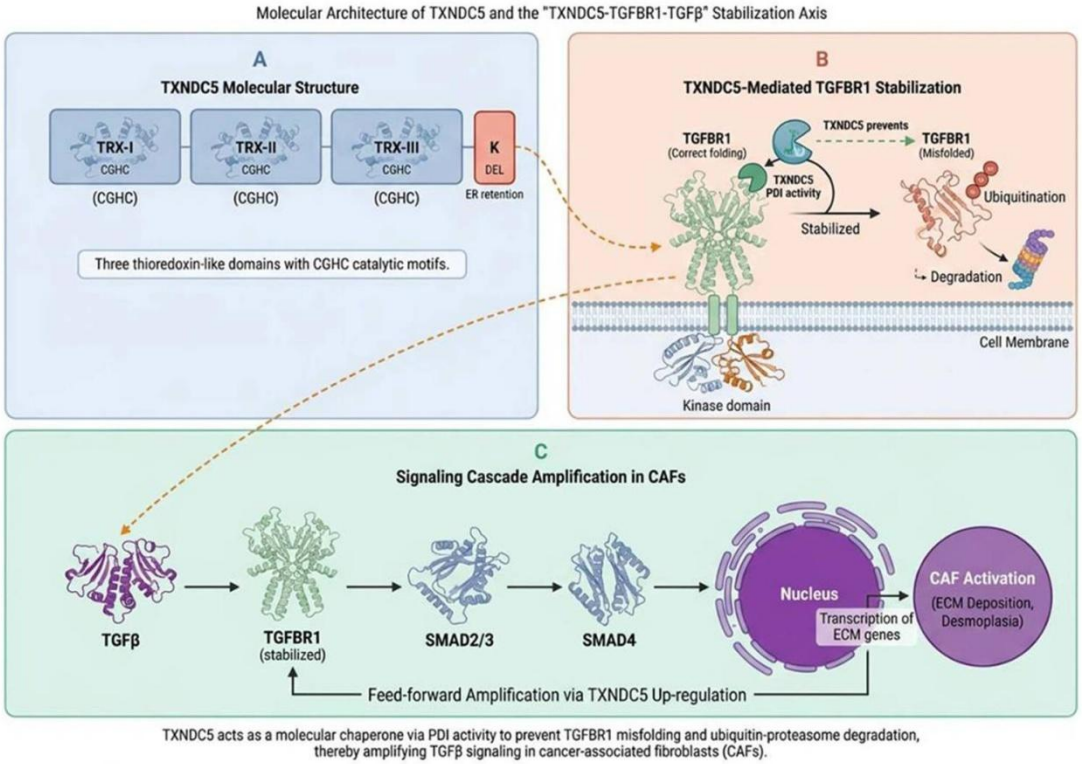

Figure 1. Molecular Architecture of TXNDC5 and the "TXNDC5-TGFBR1-TGFβ" Stabilization Axis

(A) Domain architecture of TXNDC5, illustrating three thioredoxin-like domains (TRX-I, TRX-II, TRX-III), each containing the catalytic CGHC motif, and the C-terminal KDEL sequence mediating endoplasmic reticulum retention. (B) TXNDC5-mediated stabilization of TGFBR1 through protein disulfide isomerase (PDI) activity. Under oxidative stress in the tumor microenvironment, TGFBR1 undergoes misfolding and subsequent ubiquitination by E3 ligases (e.g., Smurf2), leading to proteasomal degradation. TXNDC5 catalyzes correct disulfide bond formation, preventing misfolding and maintaining TGFBR1 surface expression and signaling competence. (C) Feed-forward amplification of TGFβ signaling in cancer-associated fibroblasts (CAFs). TGFβ binding to stabilized TGFBR1 activates canonical SMAD2/3-SMAD4 signaling, driving nuclear transcription of ECM genes (COL1A1, COL1A2, FN1, VIM) and CAF activation. TGFβ-induced unfolded protein response (UPR) via ATF6 upregulates TXNDC5 transcription, establishing a positive feedback loop that amplifies fibrotic signaling.

2.2 Expression Regulation Mechanisms

TXNDC5 expression is regulated at multiple levels, reflecting its integration into diverse cellular signaling networks. At the transcriptional level, TGFβ signaling activates the unfolded protein response (UPR) transducer ATF6, which directly upregulates TXNDC5 transcription[14]. This establishes a feed-forward loop wherein TGFβ induces TXNDC5, which in turn amplifies TGFβ signaling through TGFBR1

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stabilization[13].

At the post-transcriptional level, N6-methyladenosine (m6A) RNA modification plays a critical regulatory role. In gastric cancer, the RNA demethylase ALKBH5-mediated m6A demethylation of TXNDC5 mRNA enhances its stability and promotes malignant progression[8]. Peng et al. demonstrated that ALKBH5 directly binds to TXNDC5 mRNA and demethylates specific m6A sites, thereby enhancing mRNA stability and promoting sustained TXNDC5 protein expression[8]. This post-transcriptional stabilization mechanism bypasses transcriptional regulation and ensures robust TXNDC5 expression even under conditions where transcriptional activation may be limited. Conversely, METTL3-mediated m6A methylation has been implicated in regulating TXNDC5 expression in cervical cancer, where the ETS1 transcription factor recruits P300 and WDR5 to mediate H3K27ac and H3K4me3 histone modifications at the METTL3 promoter, leading to METTL3 upregulation and subsequent TXNDC5 expression in an m6A reader-dependent manner [15]. In acral melanoma, METTL3-mediated m6A methylation also regulates TXNDC5 expression [4], highlighting the context-dependent nature of m6A regulation. Beyond m6A modification, DNA methylation patterns at the TXNDC5 promoter region and histone modifications such as H3K27ac contribute to its tissue-specific expression and cancer-associated upregulation [1]. Non-coding RNAs, including circular RNAs such as circ_0000517 (also known as circRNA-104718) in hepatocellular carcinoma, participate in TXNDC5 regulation through competing endogenous RNA mechanisms that sponge microRNAs (miR-218-5p) targeting TXNDC5 mRNA [16].

2.3 Cellular Functional Diversity

TXNDC5 contributes to multiple cellular processes beyond protein folding. It provides antioxidant defense by maintaining the redox balance within the endoplasmic reticulum and protecting cells against oxidative stress-induced damage [17]. TXNDC5 also exhibits anti-apoptotic properties by modulating endoplasmic reticulum stress responses and preventing stress-induced cell death [18]. Additionally, TXNDC5 promotes angiogenesis through its expression in endothelial cells and its role in vascular remodeling [19]. In inflammatory contexts, TXNDC5 can modulate NF-κB signaling pathways, thereby influencing cytokine production and immune cell recruitment[11]. This functional diversity underscores TXNDC5's capacity to influence both tumor cell survival and microenvironment composition [13, 20].

3. The Dual Role of TXNDC5 in Cancer: From Direct Oncogenesis to Microenvironment Remodeling

TXNDC5 exerts its pro-tumorigenic effects through two spatially and functionally distinct but mechanistically linked pathways, which we collectively term the “Dual-Bridge” mechanism[1,5].

3.1 The Intracellular Bridge: Cell-Autonomous Pro-Tumorigenic Effects

3.1.1 Aberrant Expression and Clinical Correlations

TXNDC5 is aberrantly overexpressed in multiple malignancies, including cervical cancer, gastric cancer, colorectal cancer, hepatocellular carcinoma, and prostate cancer[21–25]. Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) in the TXNDC5 locus associated with cancer susceptibility, further supporting its role as a bona fide cancer-related gene[26]. In many tumor types, elevated TXNDC5 expression correlates with advanced disease stage, increased metastatic potential, and poor patient prognosis[27-29].

3.1.2 Pro-Tumorigenic Mechanisms

The oncogenic functions of TXNDC5 operate through diverse molecular mechanisms. In gastric cancer, the ALKBH5-m6A-TXNDC5 axis promotes tumor cell proliferation, migration, and invasion by enhancing TXNDC5 mRNA stability[8]. In prostate cancer, particularly castration-resistant prostate cancer (CRPC), TXNDC5 directly interacts with the androgen receptor (AR) protein, increasing its stability and enhancing transcriptional activity, thereby driving hormone-independent tumor growth[25]. In hepatocellular carcinoma, the circ_0000517/miR-1296-5p axis relieves post-transcriptional suppression of TXNDC5, facilitating tumor progression[23]. In cervical cancer, TXNDC5 downregulates SERPINF1 and TRAF1 expression to stimulate cell migration, vasculogenic mimicry, and angiogenesis[19]. These cell-autonomous mechanisms demonstrate TXNDC5's capacity to directly promote malignant phenotypes through diverse signaling pathways[3].

3.1.3 Protection Against Cellular Stress

TXNDC5 endows tumor cells with significant survival advantages under stressful conditions. By maintaining endoplasmic reticulum proteostasis, TXNDC5 enables tumor cells to adapt to endoplasmic reticulum stress induced by rapid proliferation and hypoxia[18]. Under hypoxic conditions, TXNDC5 expression is further upregulated through HIF-1α-mediated mechanisms, creating a positive feedback loop that enhances tumor cell survival in oxygen-deprived microenvironments[18]. This stress-protective function is particularly relevant in the context of chemotherapy resistance, as TXNDC5-mediated cytoprotection can diminish the efficacy of therapeutic agents that induce endoplasmic reticulum stress or oxidative damage[25]. Additionally, TXNDC5 may influence cancer stem cell populations by maintaining proteostasis in the specialized hypoxic niches where these cells reside, thereby supporting self-renewal capacity and therapy resistance[25].

The dichotomy of TXNDC5 function is visually summarized in Figure 2. Panel A illustrates cell-autonomous pathways wherein tumor cell-derived TXNDC5 directly promotes proliferation, AR signaling, and stress resistance. Panel B depicts non-cell-autonomous mechanisms whereby CAF-specific TXNDC5 upregulation acts as a molecular switch, stabilizing TGFBR1, amplifying paracrine TGF-β signaling,

and driving ECM deposition and immune exclusion. This dual functionality positions TXNDC5 as a unique hub bridging intrinsic tumor cell biology and extrinsic microenvironment remodeling.

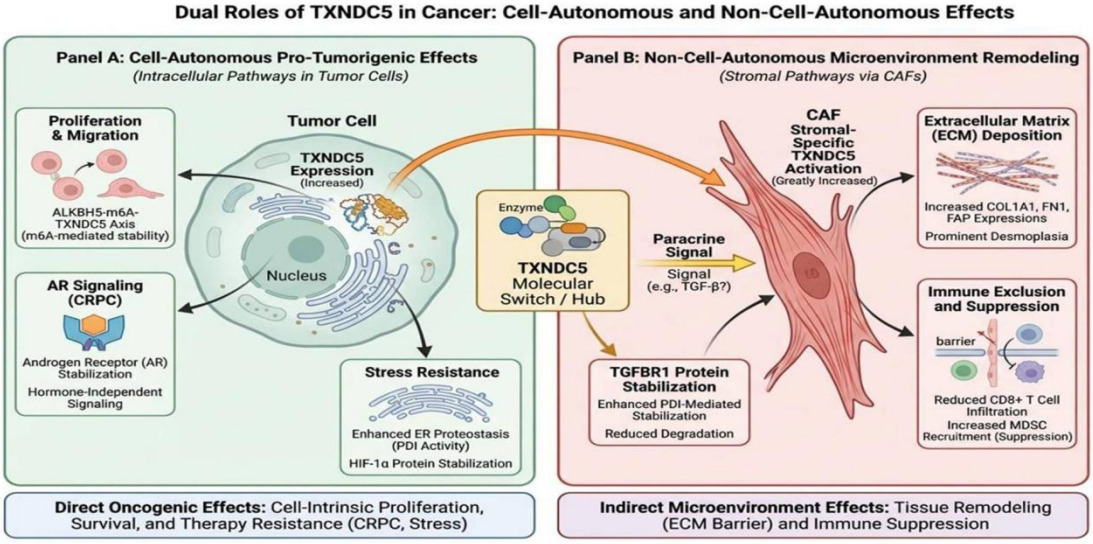

Figure 2. Dual Roles of TXNDC5 in Cancer: Cell-Autonomous and Non-Cell-Autonomous Effects

Panel A: Cell-autonomous pro-tumorigenic effects (intracellular pathways in tumor cells). Elevated TXNDC5 expression in tumor cells directly promotes malignant phenotypes through multiple mechanisms: (1) the ALKBH5-m6A-TXNDC5 axis enhances mRNA stability, driving proliferation and migration; (2) androgen receptor (AR) stabilization in castration-resistant prostate cancer (CRPC) enables hormone-independent signaling; (3) enhanced endoplasmic reticulum proteostasis via PDI activity and HIF-1α protein stabilization confers stress resistance and survival advantages under hypoxic conditions. Panel B: Non-cell-autonomous microenvironment remodeling (stromal pathways via CAFs). CAF-specific TXNDC5 upregulation (greatly increased compared to tumor cells) acts as a molecular switch/hub that: (1) stabilizes TGFBR1 through enhanced PDI-mediated disulfide bond maintenance, reducing receptor degradation; (2) drives paracrine signaling (e.g., TGF-β) that amplifies CAF activation; (3) promotes extracellular matrix (ECM) deposition with increased COL1A1, FN1, and FAP expressions, generating prominent desmoplasia; and (4) establishes immune exclusion and suppression through reduced CD8+ T cell infiltration and increased MDSC recruitment. Bottom panels summarize the dichotomy: direct oncogenic effects (cell-intrinsic proliferation, survival, and therapy resistance) versus indirect microenvironment effects (tissue remodeling and immune suppression).

3.2 The Extracellular Bridge: Microenvironment Remodeling Through Cancer-Associated Fibroblasts

While the intracellular bridge directly drives tumor cell malignancy, the extracellular bridge operates through CAF-mediated remodeling of the tumor microenvironment, representing a non-cell-autonomous pathway that is equally critical for tumor progression and therapy resistance.

3.2.1 Conceptual Migration from Organ Fibrosis to Tumor Fibrosis

The recognition of TXNDC5 as a critical mediator in organ fibrosis has provided a conceptual paradigm for understanding its role in tumor stromal remodeling. In organ fibrosis, TXNDC5 functions through PDI-mediated stabilization of TGFBR1, thereby amplifying TGFβ signaling and promoting myofibroblast activation and ECM deposition. This mechanism has been validated across multiple organ systems: in cardiac fibrosis through JNK non-canonical pathways[14]; in pulmonary fibrosis through SMAD3 canonical pathways combined with JNK/ERK signaling[7]; in renal fibrosis through SMAD3 and TGFBR1 stabilization[30]; and in hepatic fibrosis through JNK/STAT3 pathways[31]. The remarkable conservation of this mechanism across different fibrotic diseases provides a strong rationale for its extension to tumor microenvironment biology. The cross-organ conservation suggests that therapeutic strategies targeting TXNDC5 developed in one disease context may have broader applicability, particularly in oncology where insights from cardiac and pulmonary fibrosis research have already informed the understanding of cancer-associated desmoplasia [32].

3.2.2 Aberrant Expression in Cancer-Associated Fibroblasts

Recent studies, notably from the National Taiwan University team led by Dr. Lin Zhang, have demonstrated that TXNDC5 is predominantly expressed in stromal fibroblasts rather than tumor cells in mesenchymal-type colorectal cancer, a subtype characterized by extensive stromal infiltration and immune tolerance [5]. Single-cell RNA sequencing analyses have revealed that tumor-specific CAF subpopulations exhibit exceptionally high TXNDC5 expression, distinguishing them from normal tissue fibroblasts [33]. TXNDC5-high CAFs exhibit enriched expression of ECM-related genes including COL1A1, COL1A2, COL3A1, FN1, and VIM, consistent with an active matrix-producing myofibroblast phenotype. These cells also show elevated expression of TGFβ pathway genes, including TGFB1, TGFBR1, and downstream effectors SMAD2 and SMAD3, confirming the functional relevance of the TXNDC5-TGFBR1 axis [34]. This CAF-restricted expression pattern suggests that TXNDC5 functions as a stromal-specific driver of tumor progression, potentially explaining why mesenchymal-type tumors with abundant CAF infiltration exhibit particularly aggressive behavior and therapy resistance[5].

3.2.3 The "TXNDC5-TGFBR1-TGFβ" Signaling Axis

The central mechanism underlying TXNDC5-mediated CAF activation involves direct protein-protein interaction between TXNDC5 and TGFBR1[7,30]. TGFBR1, a transmembrane serine/threonine kinase receptor[35], contains multiple cysteine residues within its extracellular domain that form structurally critical disulfide bonds. Under normal physiological conditions, these disulfide bonds maintain the receptor's conformational integrity and ligand-binding affinity. However, under conditions of

oxidative stress or aberrant redox homeostasis characteristic of the tumor microenvironment, improper disulfide bond formation can lead to TGFBR1 misfolding and subsequent recognition by the ubiquitin-proteasome system for degradation[7,30].

Through its three thioredoxin domains, TXNDC5 directly interacts with TGFBR1 to catalyze the correct formation and isomerization of these critical disulfide bonds[7,30]. This chaperone-like activity prevents the accumulation of misfolded TGFBR1 and its subsequent ubiquitination by E3 ligases such as Smurf2[36]. The stabilized TGFBR1 maintains its surface expression and signaling competence, thereby amplifying CAF responsiveness to TGFβ stimulation[5]. The specificity of TXNDC5 for TGFBR1 among the TGFβ receptor family members appears to be dictated by the unique cysteine pattern and secondary structure of TGFBR1's extracellular domain[7]. This substrate specificity, combined with TXNDC5's upregulation in CAFs under TGFβ and hypoxic stimulation[14,18], creates a tissue-specific amplification loop that is particularly active in fibrotic tumor microenvironments[5,31].

Experimental evidence from fibroblast-specific TXNDC5 knockout models has definitively established that TXNDC5 is indispensable for TGFβ signaling activation in CAFs[5]. Genetic deletion of TXNDC5 markedly attenuates TGFβ-induced fibroblast activation and ECM remodeling[7,30]. The AOM/DSS colorectal cancer model has been particularly valuable for studying TXNDC5 in inflammation-driven tumorigenesis, where fibroblast-specific knockout using Coll1a2-Cre/ERT2 drivers has demonstrated the causal role of CAF-derived TXNDC5 in tumor progression and immune evasion[5].

3.2.4 Desmoplasia and Extracellular Matrix Remodeling

Activated CAFs overexpressing TXNDC5 produce excessive amounts of ECM proteins, including collagen types I and III, fibronectin, and vitronectin[37,38]. This pathological ECM deposition results in desmoplasia—a dense, scar-like stromal reaction characterized by increased matrix stiffness and altered biochemical composition[38]. The desmoplastic stroma not only provides a physical scaffold for tumor growth but also creates a biochemical barrier that sequesters growth factors, immobilizes cytokines, and establishes a pro-tumorigenic signaling microenvironment[38,39]. Increased ECM cross-linking further elevates matrix stiffness, which can directly promote tumor cell proliferation, invasion, and therapy resistance through mechanotransduction pathways[38,40,41].

4. TXNDC5-Driven Fibrotic Cascade: From Physical Barrier to Cold Tumor

4.1 Physical Effects of the Fibrotic Barrier

Figure 3 provides a comprehensive schematic of the TXNDC5-driven

fibrotic-immunosuppressive positive feedback loop that generates the cold tumor phenotype. The cascade initiates with TGFβ/hypoxia/ER stress-induced TXNDC5 upregulation in CAFs (Panel A) [5,14,18], progresses through ECM barrier formation and vascular compression (Panel B) [42], establishes an immunosuppressive network dominated by MDSCs, M2 TAMs, and Tregs (Panel C) [43], and culminates in the cold tumor phenotype with ICI resistance (Panel D) [5,44].

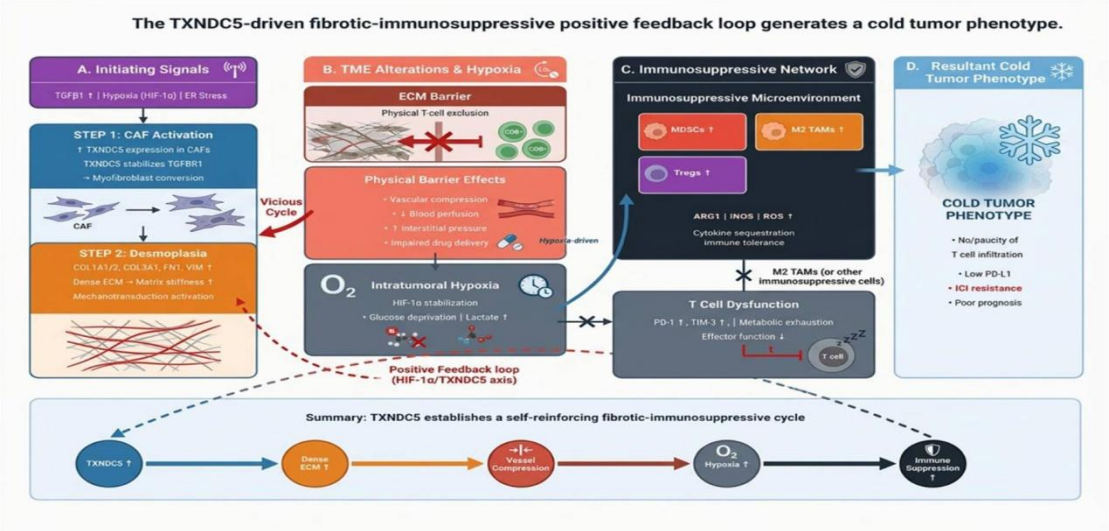

Figure 3. The TXNDC5-Driven Fibrotic-Immunosuppressive Positive Feedback Loop Generates a Cold Tumor Phenotype

(A) Initiating signals: TGFβ upregulation, hypoxia (HIF-1α stabilization), and endoplasmic reticulum stress induce TXNDC5 expression in cancer-associated fibroblasts (CAFs). (B) TME alterations and hypoxia: TXNDC5-stabilized TGFBR1 drives myofibroblast conversion and excessive ECM deposition (COL1A1/2, COL3A1, FN1, VIM), generating a dense desmoplastic stroma. The ECM barrier physically excludes CD8+ cytotoxic T lymphocytes, while increased matrix stiffness and CAF contractility compress tumor vasculature, reducing blood perfusion and elevating interstitial pressure. Vascular dysfunction exacerbates intratumoral hypoxia, stabilizing HIF-1α and further upregulating TXNDC5—a vicious positive feedback cycle. (C) Immunosuppressive network: Hypoxia-driven metabolic reprogramming recruits and expands myeloid-derived suppressor cells (MDSCs), M2-polarized tumor-associated macrophages (TAMs), and regulatory T cells (Tregs), which secrete ARG1, iNOS, and ROS to suppress effector T cell function. T cells that penetrate the fibrotic barrier undergo metabolic exhaustion with upregulated PD-1 and TIM-3. (D) Resultant cold tumor phenotype: The net outcome is an immune-excluded microenvironment characterized by paucity of T cell infiltration, low PD-L1 expression, and primary resistance to immune checkpoint inhibitors (ICIs), conferring poor prognosis. Bottom panel summarizes the self-reinforcing cycle: TXNDC5↑ → ECM deposition↑ → vascular compression → hypoxia↑ → immune suppression↑ → TXNDC5↑.

4.1.1 Tumor Vascular Compression

The dense desmoplastic stroma generated by TXNDC5-activated CAFs exerts substantial mechanical pressure on tumor vasculature [5,42]. The elevated interstitial pressure within the fibrotic tumor mass compresses blood vessels, causing vessel

distortion, collapse, and reduced perfusion [42,45]. This vascular compression is not merely a passive consequence of ECM accumulation but represents an active process whereby CAF contractility, mediated by TXNDC5-enhanced TGFβ signaling, directly constricts vascular channels [5,42]. The resulting vascular dysfunction severely impairs blood flow and creates regions of profound hypoxia within the tumor [45].

4.1.2 Exacerbation of Intratumoral Hypoxia

Vascular compression leads to inadequate tissue perfusion and progressive oxygen depletion. The resulting hypoxia stabilizes hypoxia-inducible factor-1α (HIF-1α), which transcriptionally upregulates multiple pro-tumorigenic genes and further induces TXNDC5 expression [18]. This establishes a vicious positive feedback loop: TXNDC5 drives fibrosis, fibrosis compresses vessels, hypoxia induces HIF-1α, and HIF-1α upregulates TXNDC5[5,18]. This self-reinforcing cycle progressively worsens the physical and metabolic barriers within the tumor microenvironment. The altered metabolic landscape includes glucose deprivation due to restricted diffusion, lactate accumulation from hypoxia-driven glycolysis, and amino acid depletion through consumption by activated CAFs and immunosuppressive cells[46]. These metabolic changes create a hostile environment for anti-tumor immune cells while paradoxically supporting tumor cell survival through TXNDC5-mediated stress adaptation[46,47]. This self-reinforcing cycle is visually summarized in the bottom panel of Figure 3, depicting the sequential progression from TXNDC5 upregulation to ECM deposition, vascular compression, hypoxia, immune suppression, and back to TXNDC5 induction[5].

4.2 Hypoxia-Driven Immune Suppression

4.2.1 Reprogramming of Immune Cell Populations

Hypoxic conditions within the fibrotic tumor microenvironment profoundly alter immune cell composition and function[48]. Myeloid-derived suppressor cells (MDSCs) are actively recruited and expanded under hypoxic conditions, where they suppress T cell responses and promote tumor immune tolerance[49]. Tumor-associated macrophages (TAMs) undergo polarization toward the M2 immunosuppressive phenotype, characterized by enhanced expression of anti-inflammatory cytokines and reduced antigen presentation capacity[50]. Regulatory T cells (Treg) accumulate within the hypoxic niche, further dampening anti-tumor immunity through direct suppression of effector T cells[43]. Single-cell transcriptomic analyses have revealed that in tumors with high TXNDC5-expressing CAFs, immune cell landscapes are dominated by these immunosuppressive populations, with MDSCs exhibiting expanded clonal diversity and enhanced expression of arginase-1 (ARG1), inducible nitric oxide synthase (iNOS), and reactive oxygen species generating enzymes[5,49].

4.2.2 T Cell Dysfunction

The fibrotic and hypoxic microenvironment creates multiple barriers to effective T cell-mediated anti-tumor immunity. CD8+ cytotoxic T lymphocytes, the primary effectors of anti-tumor immunity, exhibit markedly reduced infiltration into desmoplastic tumors due to physical exclusion by the dense ECM barrier[51,52]. T cells that do penetrate the fibrotic stroma encounter hypoxic conditions that induce metabolic reprogramming toward glycolysis, impairing their effector functions and promoting exhaustion[47,53]. These exhausted T cells upregulate inhibitory receptors including PD-1 and TIM-3, rendering them dysfunctional even in the presence of immune checkpoint inhibitors[53]. The net result is the formation of an immune-excluded microenvironment devoid of functional anti-tumor immunity[44,54].

4.3 Formation of the "Cold Tumor" Phenotype

4.3.1 Definition and Characteristics of Cold Tumors

Cold tumors represent a distinct immunological subtype characterized by the absence or paucity of T cell infiltration, low expression of immune checkpoint molecules, and intrinsic resistance to immune checkpoint blockade therapy[44,55]. Unlike "hot" tumors that exhibit robust T cell infiltration and respond to immunotherapy, cold tumors lack the prerequisite immune effectors necessary for checkpoint inhibitor-mediated reactivation[44]. The cold tumor phenotype represents a major clinical challenge, as the majority of solid tumors fall into this category and fail to respond to current immunotherapeutic strategies[55,56].

4.3.2 TXNDC5 as a Mediator of Cold Tumor Formation

Emerging evidence from preclinical models has established TXNDC5 as a critical mediator of cold tumor formation[5]. In mesenchymal-type colorectal cancer, fibroblast-specific deletion of TXNDC5 resulted in dramatic remodeling of the tumor immune landscape[5]. Single-cell transcriptomic analyses revealed a shift from myeloid-dominated immune suppression toward cytotoxic T lymphocyte-mediated anti-tumor immunity following TXNDC5 ablation. Specifically, TXNDC5 deletion reduced MDSC accumulation, increased CD8+ T cell infiltration, and restored T cell effector functions[5]. Importantly, TXNDC5-depleted tumors transitioned from a cold to a hot immunophenotype, acquiring sensitivity to anti-PD-1 therapy that was previously ineffective. These findings establish TXNDC5 as a molecular switch governing the transition between cold and hot tumor states[5,55]. The mechanistic basis for this immune transition involves reduced desmoplasia, decompression of tumor blood vessels, improved oxygenation, and enhanced T cell trafficking[5,45,52,57].

5. Impact of TXNDC5 on Therapeutic Efficacy

5.1 Resistance to Immune Checkpoint Inhibitors

5.1.1 Mechanisms Underlying PD-1/PD-L1 Blockade Resistance

The fibrotic barrier created by TXNDC5-activated CAFs limits the efficacy of immune checkpoint inhibitors through multiple mechanisms[5,58]. First, the physical ECM barrier prevents T cells from accessing tumor cells, rendering checkpoint blockade ineffective due to the absence of target cells within the tumor bed[58,59]. Second, even if checkpoint blockade successfully reactivates circulating T cells, the desmoplastic stroma prevents their infiltration into tumor nests[58,59]. Third, the immunosuppressive microenvironment dominated by MDSCs, M2 macrophages, and Tregs actively suppresses any residual T cell activity[60-63]. Consequently, tumors with high TXNDC5 expression and extensive desmoplasia exhibit primary resistance to PD-1/PD-L1 blockade[5,58,64,65].

5.1.2 Preclinical Evidence for Sensitization Strategies

Fibroblast-specific TXNDC5 knockout in mesenchymal-type colorectal cancer models has demonstrated remarkable synergy with anti-PD-1 therapy[5]. Tumors that were refractory to checkpoint blockade alone exhibited significant regression when combined with TXNDC5 deletion[5]. This sensitization was attributable to the combined effects of reduced desmoplasia, improved vascular perfusion, enhanced T cell infiltration, and restoration of T cell cytotoxicity[5,59]. These preclinical findings provide compelling rationale for developing TXNDC5-targeted therapies as adjuncts to immunotherapy in desmoplastic tumors[5,66].

5.2 Impact on Chemotherapy and Targeted Therapy

5.2.1 Physical Barrier-Mediated Drug Delivery Limitations

The dense ECM barrier created by TXNDC5-driven desmoplasia severely impairs drug delivery to tumor cells[5,67]. The high interstitial pressure within fibrotic tumors reduces convective drug transport, while the excessive ECM deposition increases diffusional barriers[67]. Small molecule chemotherapeutics, including 5-fluorouracil and oxaliplatin, exhibit reduced tumor penetration and efficacy in desmoplastic tumors[68,69]. Similarly, targeted therapies face physical obstacles that limit their access to tumor cells, diminishing therapeutic responses[67,70].

5.2.2 Tumor Cell-Intrinsic Resistance Mechanisms

Beyond physical barriers, TXNDC5 confers cell-intrinsic resistance to chemotherapy through its cytoprotective functions[5,70]. TXNDC5-mediated endoplasmic reticulum

stress adaptation protects tumor cells against chemotherapy-induced apoptosis[5,71]. Its antioxidant properties mitigate the oxidative damage induced by multiple chemotherapeutic agents[5,72]. Consequently, TXNDC5-overexpressing tumor cells exhibit reduced sensitivity to conventional cytotoxic therapies, necessitating higher drug doses or combination strategies to achieve therapeutic efficacy[70,73].

5.3 Impact on Anti-Angiogenic Therapy

The vascular compression induced by TXNDC5-driven desmoplasia paradoxically reduces the efficacy of anti-angiogenic therapies[67,74]. While these agents are designed to inhibit tumor vascularization, the pre-existing vascular compression caused by fibrotic stroma limits drug delivery to the tumor[67,74]. Furthermore, the hypoxia-driven compensatory angiogenic signaling may bypass the targeted pathways[74,75]. Targeting TXNDC5 to decompress tumor vessels could potentially improve the delivery and efficacy of both anti-angiogenic agents and conventional chemotherapeutics[5,67,76]. The multifaceted resistance mechanisms and corresponding reversal strategies are systematically depicted in Figure 4. The upper panel illustrates primary resistance to ICIs, chemotherapy, targeted therapy, and anti-angiogenic agents in TXNDC5-high desmoplastic tumors[64,65,74]. The middle panel outlines TXNDC5 targeting strategies and their stromal remodeling-mediated reversal effects, including cold-to-hot tumor conversion[5,66]. The bottom panel presents a proposed clinical development framework from Phase I through biomarker validation[5,66,76].

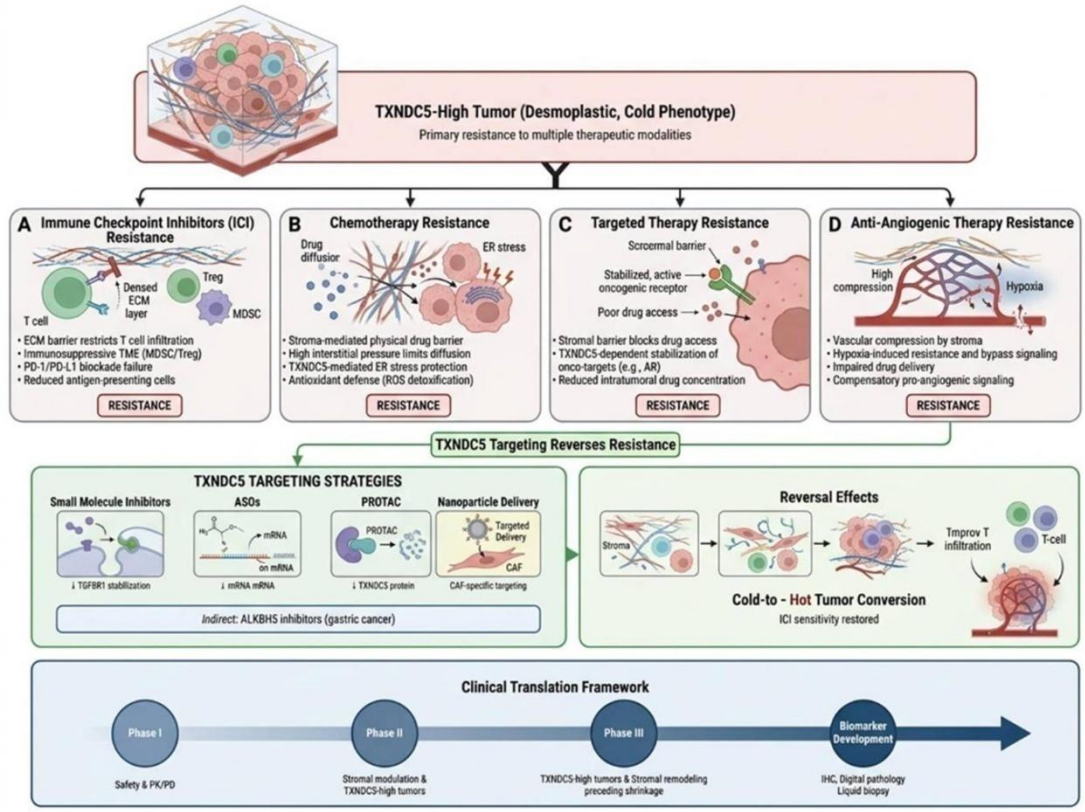

Figure 4. TXNDC5-Mediated Therapeutic Resistance and Targeted Reversal Strategies
Top panel: TXNDC5-high tumors exhibit a desmoplastic, cold phenotype with primary resistance to multiple therapeutic modalities. (A) Immune checkpoint inhibitor (ICI) resistance: The dense ECM barrier physically restricts T cell infiltration, while the immunosuppressive tumor microenvironment (MDSCs/Tregs) renders PD-1/PD-L1 blockade ineffective due to reduced antigen-presenting cells and absent target cells in the tumor bed. (B) Chemotherapy resistance: Stroma-mediated physical barriers limit drug diffusion; high interstitial pressure restricts convective transport; TXNDC5-mediated ER stress protection and antioxidant defense (ROS detoxification) confer cell-intrinsic resistance. (C) Targeted therapy resistance: The stromal barrier blocks drug access to oncogenic targets, while TXNDC5-dependent stabilization of receptors (e.g., AR in CRPC) maintains oncogenic signaling despite targeted inhibition. (D) Anti-angiogenic therapy resistance: Vascular compression by desmoplastic stroma limits drug delivery; hypoxia induces compensatory pro-angiogenic signaling that bypasses targeted pathways. Middle panel: TXNDC5 targeting reverses resistance through multiple strategies—small molecule inhibitors (↓ TGFBR1 stabilization), antisense oligonucleotides (ASOs; ↓ TXNDC5 mRNA), PROTAC-mediated degradation (↓ TXNDC5 protein), and nanoparticle-based CAF-specific delivery. Indirect targeting via ALKBH5 inhibitors (gastric cancer) downregulates TXNDC5 mRNA stability. Reversal effects include stromal remodeling, reduced desmoplasia, improved vascular perfusion, and enhanced T cell infiltration—converting cold tumors to hot tumors and restoring ICI sensitivity. Bottom panel: Clinical translation framework proposes Phase I (safety and PK/PD profiling), Phase II (biomarker-enriched enrollment of TXNDC5-high tumors with stromal modulation endpoints), Phase III (randomized trials in TXNDC5-high tumors, noting that stromal remodeling may precede tumor shrinkage), and biomarker development (IHC, digital pathology, liquid biopsy).

6. Therapeutic Prospects and Challenges in Targeting TXNDC5

6.1 Strategies for TXNDC5 Targeting

6.1.1 Development of Small Molecule Inhibitors

Despite the therapeutic potential, no specific small molecule inhibitors of TXNDC5 have yet entered clinical development[77]. The primary challenge lies in achieving selectivity among PDI family members, which share highly conserved catalytic domains and overlapping substrate specificities. However, advances in structure-based drug design, fragment-based screening, and virtual screening approaches offer promising avenues for identifying selective TXNDC5 antagonists[77]. The unique three-domain architecture of TXNDC5 and its specific protein-protein interactions, particularly with TGFBR1, may provide druggable interfaces distinct from other PDI family members[3]. The pharmacokinetic and pharmacodynamic properties of TXNDC5 inhibitors require careful optimization, given TXNDC5's intracellular localization in the endoplasmic reticulum, which necessitates adequate intracellular concentrations and ER retention[3,77].

6.1.2 Alternative Therapeutic Approaches

Beyond small molecule inhibition, multiple strategies could achieve TXNDC5 functional blockade. Antisense oligonucleotides (ASOs) targeting TXNDC5 mRNA could reduce its expression in CAFs[78]. PROTAC (Proteolysis Targeting Chimera) technology could selectively degrade TXNDC5 protein[79]. Nanoparticle-based drug delivery systems could achieve CAF-specific targeting while minimizing systemic toxicity[80,81]. Additionally, given the established role of ALKBH5 in regulating TXNDC5 mRNA stability in gastric cancer, ALKBH5 inhibitors represent an indirect but potentially effective strategy to downregulate TXNDC5 expression[8]. Tissue-specific delivery, particularly to CAFs within the tumor stroma, remains a critical technical challenge to achieve therapeutic efficacy while minimizing off-target effects on normal fibroblasts involved in wound healing and tissue repair[82]. Nanoparticle-based delivery systems could achieve CAF-specific targeting through collagen-binding peptides or FAP-directed ligands, minimizing systemic toxicity while maximizing stromal drug concentration (Figure 4, middle panel) [80,81].

6.2 Potential as a Biomarker

TXNDC5 exhibits significant potential as a predictive biomarker for immunotherapy response. Tumor tissue TXNDC5 expression levels, particularly in CAFs, could identify patients with desmoplastic tumors unlikely to benefit from checkpoint blockade[3,5,83]. Immunohistochemistry (IHC) represents the most accessible approach for clinical implementation, with digital pathology and machine learning-based image analysis standardizing scoring and improving reproducibility[84]. Serum or exosomal TXNDC5 measurements could provide non-invasive liquid biopsy alternatives for monitoring stromal activation and predicting therapeutic resistance[85]. Integration of TXNDC5 expression with established immune-related gene signatures could enhance the precision of patient stratification for immunotherapy and combination regimens[3,5,83].

6.3 Integration with Existing Therapeutic Paradigms and Regulatory Considerations

The incorporation of TXNDC5-targeted strategies into existing oncological treatment paradigms requires careful consideration of current standards of care. In colorectal cancer, where mesenchymal-type tumors represent a significant subset with poor immunotherapy response, TXNDC5 inhibition could be integrated into the treatment sequence for metastatic disease[86]. In pancreatic ductal adenocarcinoma, where desmoplasia is a defining feature and immunotherapy has been largely ineffective, TXNDC5-targeted therapy could be combined with existing chemotherapy regimens such as FOLFIRINOX or gemcitabine/nab-paclitaxel[87]. In hepatocellular carcinoma, where TXNDC5 is upregulated through the circ_0000517/miR-1296-5p axis, combination with existing targeted therapies such as sorafenib or lenvatinib could improve outcomes[3,23,88]. In gastric cancer, where the ALKBH5-m6A-TXNDC5

axis is well-established, TXNDC5-targeted therapy could be integrated with trastuzumab-based regimens for HER2-positive disease or with chemotherapy for HER2-negative disease[8,89].

The clinical development of TXNDC5-targeted therapeutics will require careful navigation of regulatory requirements. Phase I trials should focus on safety, tolerability, and pharmacokinetic/pharmacodynamic profiling, with close monitoring for endoplasmic reticulum dysfunction and impaired wound healing[77,82]. Phase II trials should employ biomarker-enriched designs, enrolling patients with TXNDC5-high, desmoplastic tumors and employing endpoints that capture both anti-tumor activity and stromal modulation[3,23,88]. Phase III trials will require randomized designs comparing TXNDC5-targeted combinations against standard of care in biomarker-selected populations. Given the stromal-modulating nature of TXNDC5 inhibition, traditional RECIST criteria may underestimate clinical benefit if tumor shrinkage is preceded by stromal remodeling and immune infiltration, suggesting that alternative response criteria may be warranted.

7. Conclusions and Perspectives

The multi-level regulatory architecture and its integration with tumor-type specific mechanisms and functional outputs are comprehensively mapped in Figure 5. Panel A depicts the five hierarchical control mechanisms, Panel B illustrates cancer-specific molecular axes, and Panel C summarizes the six major functional outputs. This network view underscores the context-dependent nature of TXNDC5 biology that must inform precision therapeutic strategies [2,90,91].

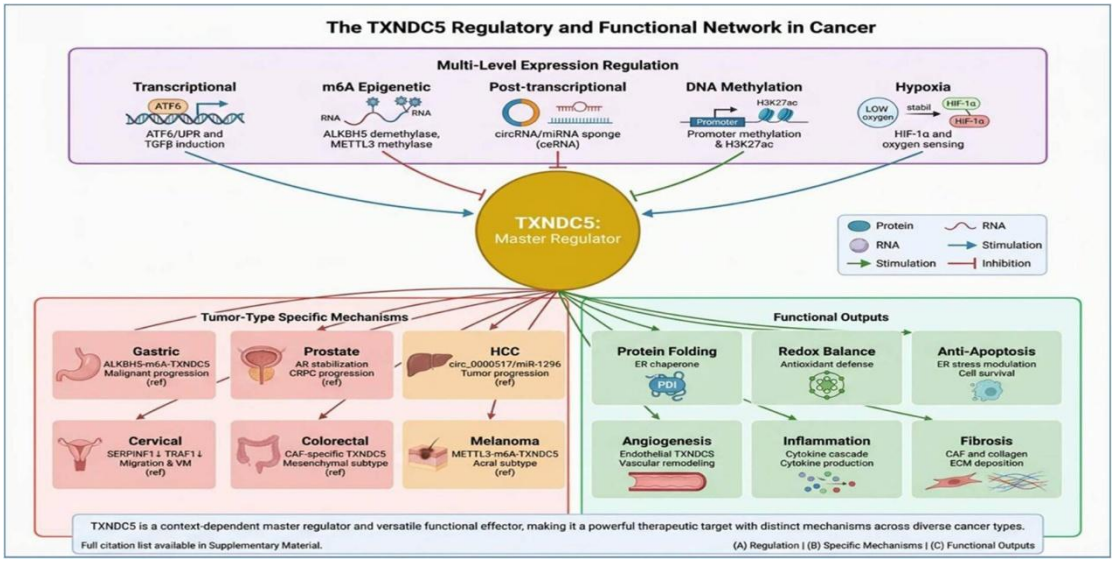

Figure 5. The TXNDC5 Regulatory and Functional Network in Cancer

(A) Multi-level expression regulation: TXNDC5 is controlled at multiple hierarchical levels—transcriptional (ATF6/UPR and TGFβ induction), m6A epigenetic (ALKBH5-mediated demethylation enhancing mRNA stability; METTL3-mediated methylation reducing stability), post-transcriptional (circRNA/miRNA sponge mechanisms, e.g., circ_0000517/miR-1296-5p in

HCC), DNA methylation (promoter methylation and H3K27ac histone modifications), and hypoxia (HIF-1α stabilization and oxygen sensing). Green arrows indicate stimulatory regulation; red blunt lines indicate inhibitory regulation. (B) Tumor-type specific mechanisms: TXNDC5 operates through distinct molecular axes across malignancies—gastric cancer (ALKBH5-m6A-TXNDC5 driving malignant progression), prostate cancer (AR stabilization in CRPC), hepatocellular carcinoma (circ_0000517/miR-1296-5p axis), cervical cancer (SERPINF1↓ and TRAF1↓ promoting migration and vasculogenic mimicry), colorectal cancer (CAF-specific TXNDC5 in mesenchymal subtype), and acral melanoma (METTL3-m6A-TXNDC5 axis). (C) Functional outputs: TXNDC5 mediates six major biological processes—protein folding (ER chaperone, PDI activity), redox balance (antioxidant defense), anti-apoptosis (ER stress modulation, cell survival), angiogenesis (endothelial TXNDC5, vascular remodeling), inflammation (NF-κB modulation, cytokine production), and fibrosis (CAF activation, collagen and ECM deposition). Bottom panel: TXNDC5 is a context-dependent master regulator and versatile functional effector, making it a powerful therapeutic target with distinct mechanisms across diverse cancer types. (A) Regulation; (B) Specific Mechanisms; (C) Functional Outputs.

TXNDC5 represents a paradigm-shifting molecular target that bridges the gap between tumor cell biology and microenvironment remodeling. Its dual functionality encompasses both cell-autonomous oncogenic effects through direct promotion of tumor cell proliferation, survival, and stress resistance[10,15,92,93], and non-cell-autonomous microenvironment remodeling through CAF activation and fibrotic stroma formation[3,5,94]. The "TXNDC5-TGFBR1-TGFβ" axis in CAFs initiates a pathological cascade that transforms the tumor microenvironment: ECM deposition leads to desmoplasia, which compresses tumor vasculature, induces hypoxia, recruits immunosuppressive cells, excludes cytotoxic T cells, and ultimately establishes the cold tumor phenotype[5,94,95]. This comprehensive framework explains why tumors with high stromal TXNDC5 expression exhibit resistance to immunotherapy, chemotherapy, and targeted therapy, and positions TXNDC5 as a master regulator of the physical and immunological tumor microenvironment[5,25,94,95].

Future research should prioritize several key areas. First, validation of TXNDC5's role in additional desmoplastic tumor types, particularly pancreatic cancer, cholangiocarcinoma, and diffuse-type gastric cancer, will establish the generalizability of the proposed mechanism[96-98]. Second, the development of selective TXNDC5 inhibitors with favorable pharmacokinetic properties represents an urgent unmet need. Third, prospective clinical studies are required to validate TXNDC5 as a predictive biomarker for immunotherapy resistance and to define optimal patient populations for TXNDC5-targeted interventions[5,31,33,99]. Fourth, deeper exploration of the cross-talk between fibrotic signaling and immune modulation may reveal additional therapeutic targets within the same pathway[100]. The integration of TXNDC5 biology into precision oncology frameworks holds the promise of converting cold tumors into hot tumors, thereby expanding the beneficiary population of cancer immunotherapy and improving outcomes for patients with currently refractory

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disease[5,95,99].

The elucidation of TXNDC5's role in tumor microenvironment remodeling represents a significant advance in our understanding of the stromal-immune-tumor axis[5,100]. By bridging the gap between organ fibrosis research and cancer biology, the TXNDC5 paradigm offers a mechanistic framework for understanding how stromal activation creates physical and immunological barriers to effective therapy[8,10,15,33,101,102]. The translational potential of TXNDC5-targeted therapy extends beyond any single tumor type, offering broad applicability in malignancies characterized by desmoplastic stroma, immune exclusion, and resistance to immunotherapy[5,94,102]. As the field advances, the integration of multi-omics profiling, advanced imaging, and artificial intelligence-based biomarker discovery will refine our ability to identify patients most likely to benefit from TXNDC5-targeted interventions, positioning TXNDC5 as a cornerstone of stromal-targeted cancer therapy[103,104].

The TXNDC5 paradigm exemplified by the Dual-Bridge framework extends beyond this single molecule. The conceptual separation of intracellular oncogenic signaling from extracellular microenvironment remodeling may apply to other PDI family members and stress-responsive proteins that exhibit dual functionality in cancer[105]. By providing a common language to describe these spatially distinct but functionally integrated pathways, the Dual-Bridge framework facilitates cross-tumor comparisons and accelerates the identification of therapeutic strategies targeting both compartments simultaneously[90]. More broadly, the Dual-Bridge framework challenges the traditional view that oncogenic drivers act solely through cell-intrinsic mechanisms. By highlighting the extracellular bridge as an equally critical pathway, this paradigm shifts the focus from tumor cell-centered models to tumor-microenvironment systems, offering a unified conceptual basis for understanding how diverse oncogenic molecules may coordinate malignancy across cellular compartments[102,103].

Declarations

Ethics approval and consent to participate

Not applicable. This is a narrative review article based on published literature and publicly available data. No original human or animal experiments, patient samples, or identifiable clinical data were included. All cited studies were previously published and comply with their respective ethical approvals and informed consent requirements..

Consent to publication

We have obtained the written consent of authors to publish in a peer-reviewed journal.

Availability of data and materials

If necessary, all data of the study can be obtained from the corresponding author of this article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Lin Zhang, Yanhong Hou, and Kai Wu conceived the study, carried out experiments, and drafted the manuscript. Yanhong Hou, Binghui Li, and Lin Zhang carried out experiments. Yanhong Hou, Binghui Li, and Lin Zhang participated in the study design and revised the manuscript.

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Authors' Information

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