PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2025, 52(9): 2217~2232
www.pibb.ac.cn

THBS4 in Disease: Mechanisms, Biomarkers, and Therapeutic Opportunities*

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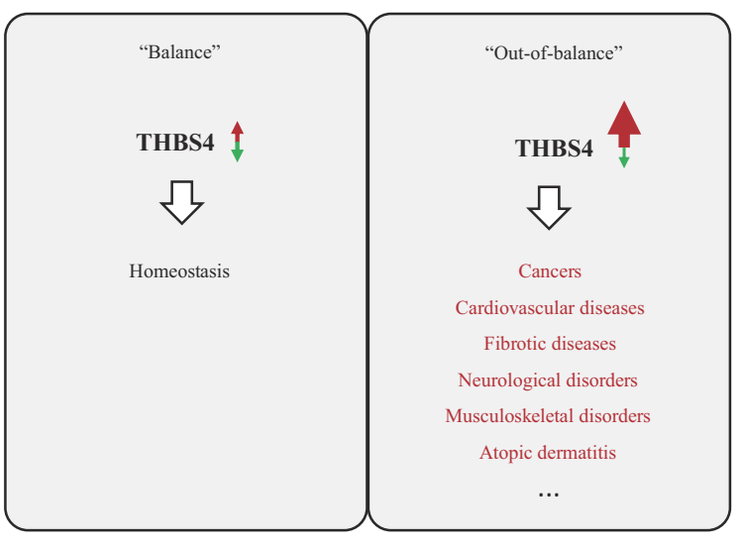
Graphical abstract



Abstract Thrombospondin 4 (THBS4; TSP4), a crucial component of the extracellular matrix (ECM), serves as an important regulator of tissue homeostasis and various pathophysiological processes. As a member of the evolutionarily conserved thrombospondin family, THBS4 is a multidomain adhesive glycoprotein characterized by six distinct structural domains that mediate its diverse biological functions. Through dynamic interactions with various ECM components, THBS4 plays pivotal roles in cell adhesion, proliferation, inflammation regulation, and tissue remodeling, establishing it as a key modulator of microenvironmental organization. The transcription and translation of *THBS4* gene, as well as the activity of the THBS4 protein, are tightly regulated by multiple signaling pathways and extracellular cues. Positive regulators of THBS4 include transforming growth factor-β (TGF-β), interferon-γ (IFNγ), granulocyte-macrophage colony-stimulating factor (GM-CSF), bone morphogenetic proteins (BMP12/13), and other regulatory factors (such as B4GALNT1, ITGA2/ITGB1, PDGFRβ, *etc*.), which upregulate THBS4 at the mRNA and/or protein level. Conversely, oxidized low-density lipoprotein (OXLDL) acts as a potent negative regulator of THBS4. This intricate regulatory

* This work was supported by a grant from Chengdu Hitech Medical Association, 2024 Special Research on Interstitial Lung Disease (2024011).
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Received: May 12, 2025 Accepted: July 11, 2025

network ensures precise spatial and temporal control of THBS4 expression in response to diverse physiological and pathological stimuli. Functionally, THBS4 acts as a critical signaling hub, influencing multiple downstream pathways essential for cellular behavior and tissue homeostasis. The best-characterized pathways include: (1) the PI3K/AKT/mTOR axis, which THBS4 modulates through both direct and indirect interactions with integrins and growth factor receptors; (2) Wnt/β-catenin signaling, where THBS4 functions as either an activator or inhibitor depending on the cellular context; (3) the suppression of DBET/TRIM69, contributing to its diverse regulatory roles. These signaling connections position THBS4 as a master regulator of cellular responses to microenvironmental changes. Substantial evidence links aberrant THBS4 expression to a range of pathological conditions, including neoplastic diseases, cardiovascular disorders, fibrotic conditions, neurodegenerative diseases, musculoskeletal disorders, and atopic dermatitis. In cancer biology, THBS4 exhibits context-dependent roles, functioning either as a tumor suppressor or promoter depending on the tumor type and microenvironment. In the cardiovascular system, THBS4 contributes to both adaptive remodeling and maladaptive fibrotic responses. Its involvement in fibrotic diseases arises from its ability to regulate ECM deposition and turnover. The diagnostic and therapeutic potential of THBS4 is particularly promising in oncology and cardiovascular medicine. As a biomarker, THBS4 expression patterns correlate significantly with disease progression and patient outcomes. Therapeutically, targeting THBS4-mediated pathways offers novel opportunities for precision medicine approaches, including anti-fibrotic therapies, modulation of the tumor microenvironment, and enhancement of tissue repair. This comprehensive review systematically explores three key aspects of THBS4 research: (1) the fundamental biological functions of THBS4 in ECM organization; (2) its mechanistic involvement in various disease pathologies; (3) its emerging potential as both a diagnostic biomarker and therapeutic target. By integrating recent insights from molecular studies, animal models, and clinical investigations, this review provides a framework for understanding the multifaceted roles of THBS4 in health and disease. The synthesis of current knowledge highlights critical research gaps and future directions for exploring THBS4-targeted interventions across multiple disease contexts. Given its unique position at the intersection of ECM biology and cellular signaling, THBS4 represents a promising frontier for the development of novel diagnostic tools and therapeutic strategies in precision medicine.

Key words thrombospondin 4, cancers, cardiovascular diseases, fibrotic diseases, targeted pharmacological

DOI：10.3724/j.pibb.2025.0226 **CSTR**：32369.14.pibb.20250226

The thrombospondin (THBS; TSP) family composes five secreted glycoproteins, including THBS1, THBS2, THBS3, THBS4, and THBS5[1-2]. These proteins play critical roles in development and disease. Although laboratory mice lacking single or multiple THBS family members remain viable and fertile, these mice show inadequate adaptability under stressful conditions[3]. The important THBS family member THBS4 was first reported in 1993[4], the *THBS4* gene, located on human chromosome 5q13, encodes a 104 ku Ca^{2+}-binding glycoprotein that participates in various biological progresses, including fibrosis, tissue remodeling, angiogenesis, inflammation, and neurite growth synaptogenesis[5]. In recent years, significant progress has made in understanding the role of THBS4, which is known to be highly expressed in cardiovascular diseases, fibrotic disorders, and cancer. This growing body of knowledge has revealed the complex mechanisms by which THBS4 contributes to the development and progression of these conditions, thereby highlighting its potential as a therapeutic target[6].

1 The structural domains of the THBS4 protein

The THBS4 protein consists of 961 amino acids and is characterized by six evolutionary conserved functional domains. (1) signal peptide (SP): THBS4 is secreted into the extracellular matrix through a signal peptide located at the N-terminus[7-8]; (2) laminin G-like domain (LamG) : activate receptor tyrosine kinases, thereby potentiating cell adhesion and migration[9]; (3) coiled coil domain (CC): one of the principal subunit oligomerization motifs responsible for oligomerization within the endoplasmic reticulum (ER) [10]; (4) EGF Repeats domain (EGF repeats): a common motif found in secreted proteins, regulates the activation of several signaling pathways including Notch signaling[11]; (5) calcium-binding type III repeats domain (Type III Repeats) [12-13], and (6) TSP C-terminal domain (TSP-C) [13]. The structure of the THBS4 monomer is shown in Figure 1.

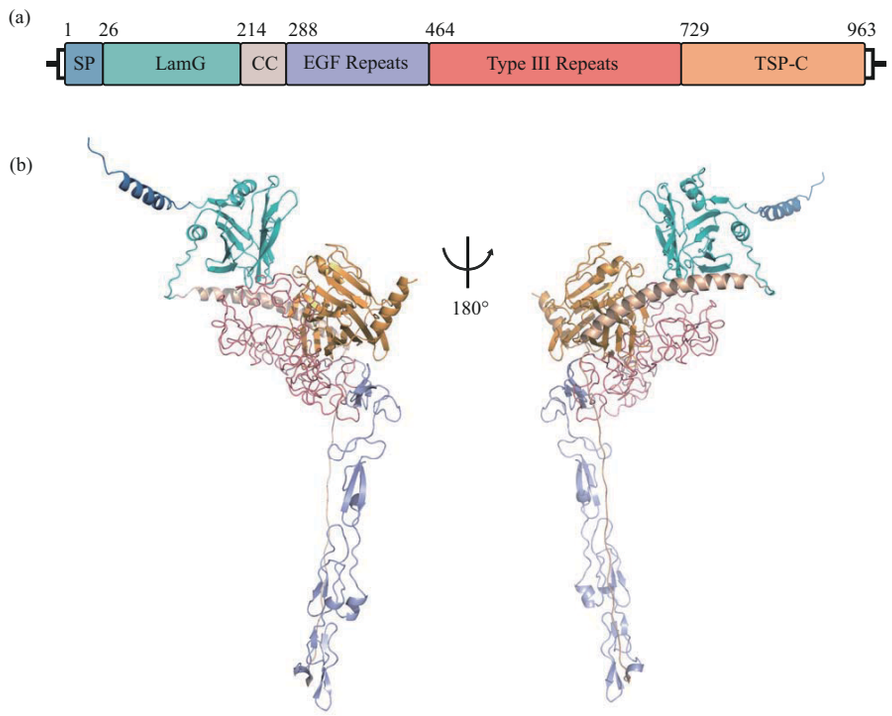

Fig. 1 Structure of THBS4

(a) Domain organization of THBS4 monomer; (b) cartoon representation of the THBS4 (AlphaFold: AF-P35443-F1).

2 Molecular regulation of THBS4 expression

Levels of THBS4 is regulated by multiple upstream signaling pathways that can either activate or inhibit its expression (Figure 2). Elucidating these regulatory mechanisms offers valuable insights into the diverse physiological and pathological functions of THBS4.

2.1 Positive regulatory mechanisms of THBS4

Multiple growth factors and transcriptional regulators positively control THBS4 expression. Among them, the transforming growth factor-β (TGF-β) signaling pathway is one of the most prominent upstream activators. In endothelial cells, TGF-β1 has been demonstrated to play a central role in regulating THBS4. Although TGF-β1 enhances the synthesis and secretion of THBS4 protein, it does not significantly upregulate its transcription[14]. This process is mediated through SMAD3, treatment with TGF-β inhibitors like SB-431542 and SMAD3 inhibitor SIS3 suppress THBS4 production[14]. In cardiac fibroblasts from diabetes (db/db) mice, upregulation of *Thbs4* is also depends on *Smad3*[15]. Additionally, TGF-β1 stimulates to increase THBS4 protein levels in endothelial cells within 24 h, simultaneously reducing THBS1 expression and leaving THBS3 levels unchanged[14]. Interestingly, the effect of TGF-β1 on THBS4 expression is cell-type specific, for example, TGF-β1 fails to induce THBS4 production in vascular smooth muscle cells[14]. In certain contexts, such as in meniscus cells, TGF-β alone is insufficient to stimulate THBS4 expression and requires cooperative signaling with BMP6 in a 3D system to achieve transcriptional activation[16].

Beyond TGF-β signaling, several other factors contribute to the upregulation of THBS4. In the context of cardiac hypertrophy, CCN2 serves as a key upstream regulator[17], whereas in dilated cardiomyopathy, JUNB and EZH2 drives *THBS4* expression[18]. The histone methyltransferase MLL4 has also been shown to epigenetically activates THBS4, thereby providing protection against pressure overload-induced heart failure[19]. In hepatocellular carcinoma (HCC), the glycosyltransferase B4GALNT1 enhances THBS4 expression[20]. Additional transcriptional activators include Mnrr1[21] and potentially WT1[22], demonstrating complex

transcriptional control.

Growth factor-mediated signaling pathways also play a prominent role in modulating THBS4. BMP12/13 signaling through ALK3 induces THBS4 expression during tendon development[23-24]. In a model of pulmonary artery banding, the tyrosine kinase inhibitor Imatinib has been shown to upregulates THBS4 *via* RUNX2[25].

2.2 Negative regulatory networks of THBS4

In contrast to activating signals, several factors can downregulate THBS4 expression. In the context of traumatic brain injury (TBI), the chemokine SDF-1 plays a role in inhibiting THBS4 expression to facilitate neuronal regeneration[26]. In macrophages, while proinflammatory stimuli (LPS, IFNγ, and GM-CSF) upregulate THBS4 expression, anti-inflammatory signals (M-CSF, IL-4) suppress its expression[27].

As noted previously, the glycosyltransferase B4GALNT1 promotes THBS4 expression in HCC[20]. Knockdown of B4GALNT1 leads to reduced THBS4 levels, while concurrently upregulating THBS1[20], suggesting coordinated regulation of thrombospondin family members.

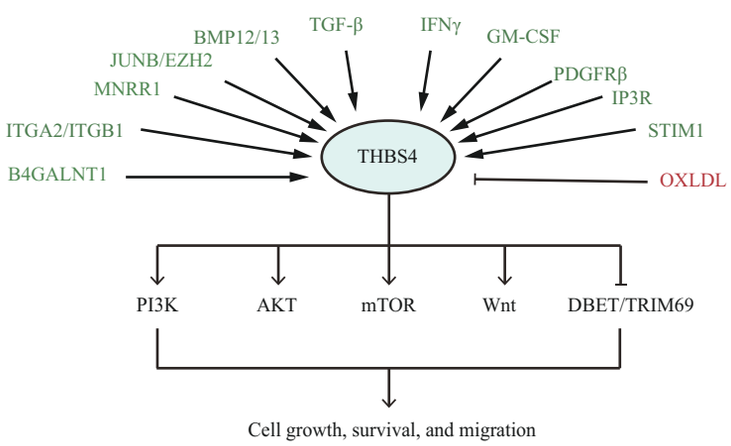

Fig. 2 The THBS4 signaling

Green: activation factors of THBS4, Red: inhibitory factor of THBS4.

3 THBS4−mediated signaling cascades

THBS4 activates downstream signaling through multiple receptor interactions (Figure 2).

3.1 Molecular interactions with cell surface receptors

In HCC, THBS4 binds integrin α2β1 to stimulate phosphorylation of PI3K/AKT/FAK[20], and also interacts with ITGB1, ITGA5 and ITGB5 to further enhance FAK/PI3K/AKT phosphorylation[28]. During wound healing, THBS4 engages ITGA2 to potentially activate Wnt/β-catenin signaling[29]. In the context of angiogenesis, THBS4 binds both integrin α2 and the gabapentin receptor α2δ-1 to enhance endothelial cell migration, with the THBS4 c.1186 G>C (p. Ala387 Pro) variant shows particularly strong activity[30]. *THBS4* can be used as a lncRNA and upregulates activation of the PI3K, AKT, and mTOR signaling pathways[31].

3.2 Diverse cellular responses and disease implications

Activated THBS4 mediates diverse cellular responses. In pulmonary artery smooth muscle cells, THBS4 enhances PI3K/AKT phosphorylation to stimulate proliferation (*via* PCNA) while inhibiting apoptosis (*via* BAX downregulation) [32]. It also mediates TGF-β-induced endothelial cell adhesion, migration and angiogenesis[14]. In macrophages, THBS4 promotes proinflammatory polarization and induces apoptosis[27]. During wound healing, activated THBS4 upregulates ANGPTL7 and FOXH1, while concurrently suppressing pathways associated with protein ubiquitination and apoptosis pathways, including DBET and TRIM69[29]. In bladder cancer, elevated THBS4 expression is associated with disease progression and poor prognosis[33]. Recombinant THBS4 (rTHBS4) has been shown to rapidly activates

AKT/MMP2 within 30 min, thereby enhancing cellular migration[33].

4 THBS4 in diseases

THBS4 is involved in the pathogenesis of various diseases, including cancer, cardiovascular disease, fibrotic disorders, neurological conditions, musculoskeletal diseases, and others. Its diverse functions are largely dictated by tissue-specific expression patterns and the complexity of associated signaling pathways.

4.1 Cancers

THBS4 is significantly upregulated across multiple tumor types. This widespread overexpression positions THBS4 as a promising therapeutic target for oncological intervention.

4.1.1 Hepatobiliary cancer

THBS4 exhibits consistent oncogenic activity in HCC[34], with significantly elevated expression in tumor tissues compared to adjacent normal liver tissue[28, 35]. Functionally, THBS4 promotes hepatocarcinogenesis by enhancing cell proliferation and invasion, as well as by maintaining cancer stemness through the support of hepatic cancer stem cells[20]. THBS4 promotes the growth of tumor models and lung metastasis in mice, whereas *sh-Thbs4* inhibits tumor growth and lung metastasis[28]. *In vitro*, THBS4 accelerates the epithelial-mesenchymal transition (EMT) and accelerates the proliferation, migration and invasion of HCC cells [28]. Clinically, THBS4 is associated with HCC-active enhancers and has been proposed as a potential diagnostic biomarker for HCC[34, 36]. Serum THBS4, in combination with other markers such as HMMR, NXPH4, and PITX1, improves the detection of AFP-negative HCC cases and aids in distinguishing HCC from benign liver disease[37].

4.1.2 Gastrointestinal cancer

In gastric cancer, *THBS4* mRNA levels are correlated with tumor volume[38], particularly in diffuse-type adenocarcinomas, where it localizes to the extracellular matrix (ECM) [8]. *THBS4* demonstrates distinct expression patterns among histological subtypes of gastric adenocarcinoma, exhibiting marked upregulation in the ECM of diffuse-type carcinomas, while being completely absent in intestinal-type tumors[8]. Genetic studies have revealed that *THBS4* single nucleotide polymorphisms (SNPs) (rs77878919/rs7736549) worsen prognosis, whereas the rs10474606 AA genotype reduces risk[38]. High *THBS4* mRNA expression is also associated with poor survival in both stage I and II gastric cancer patients[39]. In colorectal cancer, TGF-β induced PDGF-D activates THBS4 protein (but not *THBS4* mRNA) through PDGFR-β[40]. Additionally, PDGFR-β, IP3R and STIM1 also promote the post-translational modification and secretion of THBS4[40]. For cardia cancer, *THBS4* mRNA serves as a preoperative predictive marker[41].

4.1.3 Genitourinary cancer

THBS4 plays distinct yet critical roles across genitourinary malignancies, with particularly notable significant upregulation observed in prostate cancer[42]. Clinically, *THBS4* levels are positively correlated with tumor volume in prostate cancer[43], with epigenetic analyses revealing tumor tissue hypomethylation patterns[44] and obesity-associated genetic variants that collectively increase cancer risk[44]. In prostate cancer stem cells ($CD133^+$ population), THBS4 enhances self-renewal capacity *via* activation of the PI3K/AKT signaling pathway, while simultaneously reducing apoptosis and upregulating stemness markers including CD133, CD13, and OCT4[43]. In bladder cancer, elevated *THBS4* expression associates with advanced tumor progression and poorer survival outcomes[33]. Mechanistically, rTHBS4 has been shown to rapidly activates AKT/MMP2 signaling within 30 min to promote cellular migration and invasion[33]. For renal cell carcinoma, *THBS4* CpG methylation status has emerged as a valuable predictor of metastatic potential[45-46], highlighting its clinical utility across diverse genitourinary malignancies.

4.1.4 Other cancers

Lymph node metastasis in small papillary thyroid carcinoma is associated with high *THBS4* expression and an increased presence of $PDGFRA^+$ cancer-associated fibroblasts[47]. In breast cancer, *THBS4* elevates in tumor cells[48] and has been identified as a vascular/immune response marker in $HER2^+$ subtypes[49]. By contrast, *THBS4* expression is downregulated in giant fibroadenomas of the breast[50]. In cervical cancer, miR-5701 exerts tumor-suppressive effects by targeting the 3'-untranslated region (3'-UTR) of *THBS4*[51]. Within central nervous system tumors, grade I astrocytoma also shows

THBS4 upregulation[52].

4.2 Cardiovascular diseases

THBS4 plays multifaceted roles in cardiovascular diseases, with its functional effects largely determined by its spatial expression patterns and the complexity of the signaling pathways in which it is involved.

4.2.1 Genetic polymorphisms and coronary artery disease risk

Coronary artery disease (CAD) is a chronic cardiovascular condition characterized by the buildup of atherosclerotic plaques in the coronary arteries, leading to reduced myocardial blood flow and oxygen supply, which may result in angina, myocardial infarction, or heart failure[53]. The *THBS4* c.1186 G>C (p. Ala387Pro) polymorphism demonstrates complex associations with cardiovascular risk, showing a protective effect against CAD in some populations[54], while being enriched among white patients with myocardial infarction[55]. Similarly, the *THBS4* c.1186 G>C (p. Ala387Pro) variant serves as a low-risk factor for myocardial infarction in elderly women[56]. In contrast, while the THBS1 p. Asn700Ser polymorphism increases CAD risk in Asian and European populations, the *THBS4* c. 1186 G>C (p. Ala387Pro) has been linked to elevated CAD susceptibility in American cohorts[57]. Notably, the *THBS4* rs17878919 polymorphisms shows no significant association with CAD in Han Chinese population[58]. In addition to genetic factors, experimental studies have demonstrated that THBS4 increase risk of heart disease of mouse model, likely through the induction of endoplasmic reticulum stress[7, 13]

4.2.2 Atherosclerosis and vascular remodeling

THBS4 expression is elevated in the ECM of atherosclerotic plaque[59] and results in arterial injury, with knockout mice showing reduced aortic root lesions and macrophage infiltration[59]. In vascular injury models, clearance of *Thbs4* attenuates restenosis by suppressing macrophage recruitment, vascular smooth muscle cell proliferation and migration, and pro-inflammatory chemokine secretion (MCP-1, VCAM-1, ICAM-1, and IL-6) [60]. THBS4 exhibits a unique vascular specific expression pattern, being selectively expressed in veins but not in arteries[61]. In comparison, THBS3 is expressed in both veins and arteries, whereas THBS5 is expressed only in arteries[61]. Despite these tissue-specific expression differences, clinical studies have also reported that THBS4 can be used as a biomarker for the diagnosis, severity assessment, and follow-up of peripheral artery disease[62].

4.2.3 Hypertension and cardiac stress responses

THBS4 demonstrates dual roles in hypertension. It inhibits angiotensin II (AngII) -induced hypertension and protects endothelial function in AngII-induced hypertension models[63], although *Thbs4* loss of function increases the risk of aortic aneurysm[64]. Histone methyltransferase MLL4 upregulates THBS4 to mitigate pressure overload-induced heart failure[19]. In hypertensive animal models, *Thbs4* mRNA increases in arterial walls[64], with elevated levels observed post-metoprolol or acupuncture treatment in spontaneously hypertensive rats (SHRs)[65].

4.2.4 Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH), a subtype of pulmonary hypertension (PH), is characterized by pulmonary arterial pathologic remodeling[66]. In congenital heart disease-associated PAH (PAH-CHD), THBS4 expression is markedly elevated in both lung tissue and plasma, with significantly higher levels observed in patients with severe compared to mild PAH-CHD[32]. In monocrotaline-arteriovenous shunt (MCT-AV) rat models of PAH, THBS4 is upregulated in pulmonary tissues and is positively correlated with the severity of vascular pathology[32]. In this model, vascular smooth muscle cells (VSMCs) actively produce THBS4, which exerts pro-proliferative and pro-migratory effects by downregulating the expression of contractile markers (α-SMA, MYH11) and the pro-apoptotic factor BAX, while upregulating proliferating cell nuclear antigen and endothelial-mesenchymal transition (EndMT) -related N-cadherin expression[32]. Therapeutic delivery of *Thbs4*-silencing adeno-associated virus (AAV) *via* tracheal administration effectively attenuates vascular remodeling in MCT-AV rat, highlighting THBS4 as a potential therapeutic target for PAH[32].

4.3 Fibrotic diseases

THBS4 is critically involved in fibrotic processes across diverse tissues, influencing wound healing, pathological fibrosis, and tissue remodeling.

Keloids are pathological fibroproliferative lesions characterized by excessive fibroblast proliferation and ECM deposition beyond the original

wound boundaries following cutaneous injury[67]. During keloid formation, *THBS4* is significantly overexpressed alongside *THBS2* and *TGFB3*[68]. Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by vasculopathy, immune dysregulation, and progressive fibrosis affecting the skin and internal organs[69]. *THBS4*, *THBS1*, *COMP*, *FN1*, and *TNC* have been identified as hub genes within the PI3K/AKT signaling pathway during skin fibrogenesis in SSc patients[70]. Moreover, THBS4 expression levels correlate positively with the modified Rodnan skin score (mRSS), a clinical measure of skin fibrosis severity in SSc patients [70].

THBS4 is barely detectable in normal human skin but is highly expressed in the dermis of healed burn wounds, peaking at 3 days post-excision/grafting, coinciding with the proliferative phase of wound healing[29]. rTHBS4 has been shown to enhance fibroblast migration and promotes keratinocyte proliferation *in vitro*[29]. Topical application of rTHBS4 accelerates wound closure in mice[29], whereas *Thbs4* knockout (KO) delays the healing process[30]. In murine skin, THBS4 is highly expressed near proliferating $Ki67^+$ basal keratinocytes[29], further implicating its role in epidermal regeneration. In zebrafish models, THBS4 actively promotes fin regeneration[71], underscoring its fundamental role in ECM remodeling and wound healing processes across species.

THBS4 plays a multifaceted role in cardiac fibrosis across various pathological models. In transverse aortic constriction (TAC), THBS4 is localized to collagens I/IV in the ECM of cardiomyocytes[72]. While monocrotaline-induced right ventricular failure increases *THBS4* expression[73], genetic deletion of *Thbs4* paradoxically reduces fibrosis despite elevated mRNA levels of *Collagen I–V*[72]. Although *Thbs4* is upregulated in db/db cardiac fibroblasts and serves as a marker for activating fibroblasts *in vivo*[15], it lacks direct fibroblast-activating effects *in vitro*[15]. Secreted THBS4 binds ECM proteins and β1D integrins to acilitate adaptive remodeling[74-75]. As an ECM-related gene, THBS4 also defines distinct fibroblast subpopulations involved in fibrosis[76]. Single-cell transcriptomic analyses reveal expansion of $Thbs4^+$/$Cthrc1^+$ pro-fibrotic fibroblasts in pressure-overloaded hearts[77], with a similar increase observed in $THBS4^+$ fibroblasts in human ischemic cardiomyopathy[78]. Notably, *THBS4* serves as a central immune-related gene in dilated cardiomyopathy[18], and it can serve as a predictive biomarker panel for heart failure risk assessment[18, 79]. Cardiomyocyte-specific overexpression of wild-type THBS4 improves sarcolemma stability, whereas secretion-deficient THBS4-mCa^{2+} mutants exacerbate cardiomyopathy[80].

Fibrosis is the characteristic pathological manifestation of endometriosis[81]. Endometriosis is defined as the growth and invasion of functional endometrial tissue outside the uterus, and is one of the most common gynecological diseases in women of childbearing age[81]. rTHBS4 upregulates the expression of collagen I, fibronectin, α-SMA, and CTGF in a concentration-dependent manner in ectopic endometrial stromal cells[82].

4.4 Neurological disorders

THBS4 plays a multifaceted role in the nervous system, contributing to both normal neurodevelopment and neurological disorders. Its expression is dynamically regulated in astrocytes, neurons, and cerebrovascular cells, and is implicated in processes such as synaptogenesis, neuronal migration, and neurodegeneration.

During human brain evolution, *THBS4* shows increased cortical expression along with *THBS2*[83], with the highest mRNA levels observed in the frontal and temporal cortices across primates (including human, chimpanzee, rhesus macaque, and pigtail macaque) [83]. Notably, *THBS4* is localized to deeper cortical astrocytes and cerebrovascular endothelial cells[83]. *Thbs4* is also expressed in the rostral migratory stream, and its disfunction impairs neuronal migration in both juvenile and adult mice[84]. As a neuronal ECM protein secreted by neurons[85], THBS4 promotes neurite outgrowth and accumulation at adult neuromuscular junctions and synaptic-rich structures[85]. Young mouse serum containing THBS4 enhances synapse formation in cultured neurons, promoting dendritic arborization and synaptic transmission[86]. In the context of human bitter-sweet taste perception, *THBS4* is associated with total bitter beverages[87], indicating potential roles in sensory processing. *Thbs1/2* double knockdown in the nervous system results in compensatory upregulation of *Thbs4* expression[88].

Reactive astrogliosis results in high *Thbs4* expression[89], although both protein and mRNA levels decrease after cortical injury[26]. Interestingly,

anesthesia-induced hypothermia upregulates *Thbs4* in the hippocampus[90], with gene expression peaking 4 d post-anesthesia[91]. In neurological disorders, THBS4 protein aggregates at β-amyloid plaque sites in the frontal cortex and hippocampus of Alzheimer's patients[83]. In pediatric spinal muscular atrophy patients, THBS4 levels in cerebrospinal fluid prior to treatment and increase following therapeutic intervention, suggesting its potential utility as a biomarker for monitoring treatment response in these patients[92].

4.5 Musculoskeletal disorders and tissue homeostasis

THBS4 plays pivotal and context-specific roles in musculoskeletal tissues, particularly in the regulation of cartilage, tendon, and muscle homeostasis.

4.5.1 Cartilage and tendon pathophysiology

THBS4 exhibits properties that promote cartilage formation[93], while serving as a critical regulator in tendon biology. *THBS4* acts as a specific molecular marker for tendon proper-derived progenitors, enabling their distinguish tendon proper progenitors from peritenon progenitors[94]. THBS4 also functions as a mechanosensitive tenogenic marker, and is not expressed in tendon stem cells under high-stiffness conditions[95]. The functional importance of THBS4 in tendon homeostasis is evidenced by THBS4 loss-of-function models, which exhibit abnormal collagen fibril organization characterized by enlarged fibril diameter[61]. Multiple studies have confirmed that *THBS4* is a tendon-related marker[96-99] and a tendon-selective gene in both rats and humans[100]. In rats, THBS4 shows elevated expression in patellar tendon fibroblasts[101] and demonstrates distinct spatial expression patterns-co-localizing with THBS5 in the perimysium while maintaining mutually exclusive expression with THBS3 in murine tendons[61].

4.5.2 Muscular dystrophies and myopathies

In human muscular dystrophy, THBS4 expression is significantly upregulated in skeletal muscle[74], where it undergoes a dynamic cycle of expression, secretion, and reuptake by muscle fibers[74]. In mouse models of Duchenne muscular dystrophy (dystrophin deficiency) and limb girdle muscular dystrophy type 2F (lgmd2f, δ-sarcoglycan deficiency), *Thbs4* overexpression has been shown to alleviate dystrophic disease, whereas deletion of *Thbs4* gene exacerbates disease severity[102]. These findings highlight the therapeutic potential of THBS4, as its overexpression alleviates muscular dystrophy symptoms, while genetic deletion exacerbates pathology in both *Thbs4*/*Sgcd* double knockout and *Thbs4*$^{-/-}$ Mdx mouse models[74]. Dystrophinopathies and muscle glycogen deficient muscles have marked deposition of THBS4 in the ECM, whereas abnormal protein deficient muscles have redundant decorin[103]. *Thbs4* knockout studies reveal multiple muscular abnormalities, including reduced soleus muscle volume, diminished limb strength[61], downregulation of TGF-β receptor (betaglycan) expression, and impaired lipoprotein lipase activity[61]. The THBS4 protein normally localizes to triceps, tendons, and soleus endomysium, forming distinctive spherical aggregates around intramuscular capillaries[61]. Additionally, genetic studies have identified rs12521798 variant-mediated regulation of *THBS4* expression in esophageal muscle[104].

THBS4 exhibits distinct expression patterns in orthopedic conditions. *THBS4* mRNA is upregulated in osteoarthritis (OA) patients but downregulated in osteoporosis (OP) patients[105]. In canine models, THBS4 expression is also upregulated in peripheral blood of dogs with degenerative joint disease[106]. THBS4 levels are increased in the synovial fluid of patients with anterior disc displacement of temporomandibular joint disc displacement without OA[107]. Notably, *Thbs4*-knockout mice do not display skeletal abnormalities, in contrast to *Thbs3*-deficient models[61], indicating functional divergence among thrombospondin family members.

4.6 Other diseases

THBS4 is associated with a broad spectrum of diseases. In addition to the conditions mentioned above, it has also been reported to play a role in various other pathological processes.

THBS4 is upregulated in certain skin diseases. Atopic dermatitis (AD) is a common chronic, recurrent, inflammatory skin disease with epidermal barrier defects and immune dysregulation[108]. In normal human skin, THBS4 is expressed at low-levels in the dermis, minimally in the papillary dermis adjacent to the epidermal basement layer[109]. However, in AD patients, its expression is markedly elevated in dermal fibroblasts[109]. THBS4 protein stimulates keratinocytes to upregulate genes involved in proliferation, migration, inflammation, and

differentiation, including *IL37* and *TSLP*-key drivers of AD pathogenesis[109].

In chronic intermittent hypoxia mouse models, THBS4 expression is significantly increased, and THBS4 functions as a sensitive hypoxia-responsive marker[110]. Mechanistically, THBS4 participates in the PI3K/AKT signaling pathway and is elevated in ischemic-hypoxic rat plasma[111]. THBS4 levels are also significantly increased in various hematological disorders, including primary thrombocythemia, polycythemia vera, and primary myelofibrosis[112]. In reproductive endocrinology, such as in polycystic ovary syndrome (PCOS) patients, THBS4 expression is decreased in follicular fluid, with proteomic analyses revealing a positive correlation with oocyte competence[113].

In males, serum levels of THBS4 and cathepsin B differ significantly different between the physically weakest and fittest participants[114]. The levels of *THBS4* mRNA and protein are increased in patients with benign prostatic obstruction and return to the control level after transurethral resection of the prostate surgery[115]. Furthermore, THBS4 expression positively correlated with pain intensity, suggesting that THBS4 may be a new candidate for pain indicators[116].

THBS4 also plays a role in inflammatory regulation. The A387P-THBS4 knock-in mouse model demonstrates a significant reduction in peritoneal macrophages but an increased in pro-inflammatory macrophages within peritoneal tissues[27], indicating that THBS4 may modulate macrophage trafficking by promoting their retention in tissues or restricting their migration into body cavities during inflammatory responses.

In the context of substance abuse and toxicology, serum THBS4 levels are significantly elevated in cannabis-intoxicated rabbits, highlighting its potential as a novel biomarker for drug intoxication drug monitoring[117].

5 THBS4−targeted pharmacological strategies

THBS4 activity is dynamically regulated through multiple pharmacological and physiological mechanisms, as evidenced by recent findings (Table 1). The natural compound Ophiopogonin D have been identified as THBS4 inhibitors, demonstrating therapeutic potential in diseases such as hepatocellular carcinoma[20]. Oxidized low-density lipoprotein (OXLDL) reduces *Thbs4* mRNA and protein expression in mouse macrophages[118]. At the post-transcriptional level, miR-5701 negatively regulates *THBS4* expression in human cervical cancer cells by binding to the 3'-UTR of *THBS4* mRNA[51].

Several pharmacological interventions modulate THBS4 expression in disease models. In human brain microvascular endothelial cells, sodium ferulate can increase the expression of THBS4 to promote damage repair in cells[119]. In SHR models of cardiac injury, both metoprolol treatment and acupuncture therapy elevate *Thbs4* mRNA levels[65], suggesting cardioprotective mechanisms involving THBS4 upregulation. Similarly, the tyrosine kinase inhibitor Imatinib enhances THBS4 expression through RUNX2 activation in pulmonary artery banding models[25], revealing an unrecognized regulatory pathway.

Nutritional factors also influence THBS4 expression, as shown by methionine-supplemented diets that simultaneously up-regulate *Thbs4* and *Tgfb2* expression in mice[120].

Table 1 Interventions of THBS4 expression

Regulation type	Mechanism	Effector	Biological effect	Reference
Activation	Pharmacological treatment	Metoprolol/Acupuncture	↑ *THBS4* mRNA in cardiac injury	[65]
Activation	Tyrosine kinase inhibition	Imatinib (*via* Runx2)	↑ THBS4 in pulmonary artery banding	[25]
Activation	Dietary modification	Methionine supplementation	↑ THBS4 expression	[120]
Activation	Natural phenolic compound	Sodium ferulate	↑ THBS4 expression	[119]
Activation	miRNA-mediated suppression	miR-5701 inhibitor	↓ Binds *THBS4* 3'-UTR	[51]
Inactivation	Natural compound inhibition	Ophiopogonin D	↓ THBS4 expression	[20]
Inactivation	miRNA-mediated suppression	miR-5701mic	↑ Binds *THBS4* 3'-UTR	[51]

6 Potential drug targets against THBS4

The regulation of THBS4 expression begins with the binding of cytokines (including TGF-β, GM-CSF, and BMP) to receptors (*e.g.*, TGFBR1/2 and integrin α2β1)[14, 27, 29, 74]. These cytokines can be antagonized by neutralizing antibodies, such as Fresolimumab (targeting TGF-β1, -β2, or -β3)[121], Otilimab (GM-CSF antibody)[122], and Saphnelo (type I interferon receptor antibody)[123], or blocked by inhibitors like BTT-3033/BTT-3034 (integrin α2β1 inhibitors)[124]. Following receptor binding, cytokines activate kinase domains within the receptors or downstream proteins, leading to the phosphorylation of transcription factors. These factors then translocate into the nucleus to bind the THBS4 promoter and initiate transcription. Key kinase activities in this process can be disrupted by small-molecule inhibitors: Galunisertib (TGF-β receptor I kinase inhibitor)[125], 3-Methyladenine[126], Dactolisib[127], or Wortmannin (PI3K inhibitors)[128], A-674563 and CCT128930 (AKT inhibitors)[129-130], Ifebemtinib (FAK inhibitor)[131], Tofacitinib (JAK1/2/3 inhibitor)[132]. On the other hand, we can directly target *THBS4 via* siRNA, which reduces the mRNA stability of *THBS4*, or antibodies neutralize the secreted THBS4 protein. A schematic diagram of possible drug targets against THBS4 is shown in Figure 3.

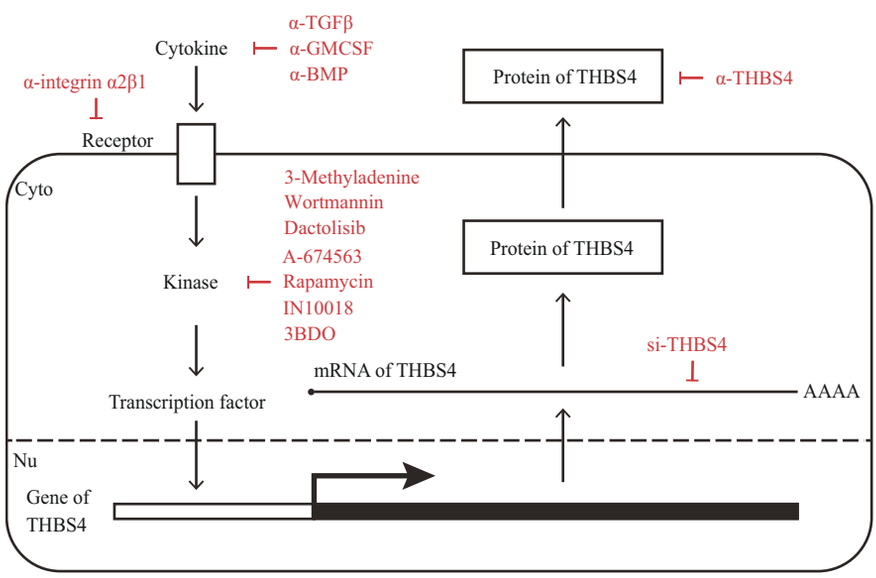

Fig. 3 Potential drug targets against THBS4

si-THBS4: siRNA of THBS4; α-THBS4: neutralizing antibody against THBS4; Cyto: cytoplasm; Nu: nucleus.

7 Conclusion

THBS4 has emerged as a critical regulator in cardiovascular diseases, fibrosis, and cancer through its multifaceted roles in extracellular matrix remodeling and immune modulation. While its functions present both challenges and opportunities, accumulating evidence positions THBS4 as a promising diagnostic biomarker and therapeutic target. Future research should focus on elucidating cell-type specific mechanisms and developing targeted interventions to harness the therapeutic potential of THBS4 while mitigating its pathogenic effects in various disease states.

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血小板反应蛋白4在疾病中的作用机制、生物标志物潜力及治疗前景*

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摘要 血小板反应蛋白4（THBS4；TSP4）是一种细胞外基质的重要组成成分，在维持组织稳态中发挥核心作用。THBS4属于血小板反应蛋白家族，这是一类进化上高度保守的多结构域黏附糖蛋白。THBS4蛋白包含6个结构域，通过与其他细胞外基质成分相互作用，在介导细胞黏附、促进细胞增殖、调节炎症反应和组织重塑过程中扮演关键角色。*THBS4*的转录及翻译受多种信号分子调控，其中，骨形态发生蛋白（bone morphogenetic protein，BMP）12/13、转化生长因子β（transforming growth factor-β，TGF-β）、γ干扰素（interferon-γ，IFN-γ）、粒细胞-巨噬细胞集落刺激因子（granulocyte-macrophage colony-stimulating factor，GM-CSF）等因子发挥促进*THBS4*基因表达的作用，而氧化性低密度脂蛋白（oxidized low-density lipoprotein，OXLDL）发挥抑制作用。THBS4的表达量及活性变化又可以影响多条下游信号的激活或关闭，包括磷脂酰肌醇3激酶（phosphatidylinositol-3-kinase，Pl3K）、蛋白激酶B（protein kinase B，PKB/AKT）、哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）、Wnt（Wingless-related integration site）信号通路。THBS4处于细胞复杂信号网络的核心位置，因此，其表达量变化及功能异常通常与多种疾病紧密相关，例如肿瘤、心血管疾病、纤维化、神经退行性疾病、肌肉骨骼疾病、特应性皮炎等。THBS4已成为疾病诊断和预后评估的潜在生物标志物及治疗靶标，尤其在肿瘤和心血管疾病领域。本文综述了当前对THBS4的生物学功能、THBS4参与疾病发生发展的相关机制及THBS4的潜在治疗靶点的研究进展。

关键词 血小板反应蛋白4，癌症，心血管疾病，纤维化疾病，靶向药理学
中图分类号 Q7，R4 **DOI**：10.3724/j.pibb.2025.0226 **CSTR**：32369.14.pibb.20250226

* 成都市高新医学会2024年间质性肺疾病专项科研基金立项课题（2024011）资助项目。
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收稿日期：2025-05-12，接受日期：2025-07-11