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LTBP2: Bridging our Understanding of the Extracellular Matrix in Cardiac Fibrosis

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Abstract

Cardiac fibrosis is a major driver of heart failure, with complex mechanisms contributing to its progression. One such contributor is latent transforming growth factor-beta binding protein-2 (LTBP2), a protein significantly upregulated in fibrotic tissues. Unlike other TGF-β binding proteins, LTBP2 does not bind to TGF-β, and its role in cardiac fibrosis is largely unexplored. However, LTBP2 is involved in key profibrotic signaling pathways, including those related to TGF-β1, fibroblast growth factor-2 (FGF-2), caspase-3, and NF-κB, all of which are potential therapeutic targets. Notably, NF-κB signaling activation through LTBP2 in fibrosis progression has been identified as an important mechanism that warrants further investigation. In addition to its role in cell signaling, LTBP2 is essential for maintaining microfibril structural integrity, particularly in tissues such as the eye. However, the specific contributions of LTBP2 and microfibrils to cardiac fibrosis remain to be fully elucidated. Furthermore, LTBP2's early-stage upregulation and its presence in circulating serum highlight its potential as a biomarker for fibrotic diseases. Studies in pulmonary fibrosis and other organ systems have demonstrated that serum LTBP2 levels correlate with fibrosis progression and the differentiation of fibroblasts to myofibroblasts. These findings suggest that LTBP2 may serve as an early indicator of cardiac fibrosis. Overall, the investigation of LTBP2's role in cardiac fibrosis is crucial for understanding its therapeutic potential and for identifying new strategies to promote reparative fibrosis and prevent the progression to heart failure.

Background of Cardiac Fibrosis

Heart diseases are a leading cause of global morbidity and mortality, affecting over 523-million individuals annually, with a rising incidence and significant economic burden.1,2 Heart failure, a progressive condition where the heart fails to meet circulatory demands, often culminates in severe outcomes. Cardiac fibrosis, a key driver of heart failure, is characterized by the replacement of dead cardiomyocytes with stiff, collagen-rich scars, impairing cardiac function.2,3

Cardiac fibrosis involves pathological remodeling of the myocardium via excessive extracellular matrix (ECM) deposition by activated cardiac fibroblasts.3-6 This process reduces myocardial compliance and is observed in conditions like myocardial infarction, hypertensive heart disease, and cardiomyopathy, all marked by cardiomyocyte death.7 The initial fibrotic response serves to stabilize myocardial structure and prevent rupture after injury, but chronic ECM remodeling by myofibroblasts leads to stiffened scars and impaired cardiac function.2,4,7-9

Cardiac fibroblasts, essential for maintaining ECM integrity, provide structural support, mediate mechanical forces, and maintain electrophysiological homeostasis.2,9 Following injury, they differentiate into myofibroblasts, driving ECM deposition and scar formation.2-4,8 Chronic activation of these cells leads to pathological fibrosis, emphasizing the need to understand the cellular and signaling mechanisms involved, which may offer therapeutic targets.

LTBP2: An ECM-Specific Modulator of Cardiac Fibrosis

Cardiac fibrosis arises from diverse causes such as injury, aging, and disease, which are difficult to target therapeutically.9 However, the activation of myofibroblasts and excessive ECM protein deposition offers potential intervention points. Controlling fibrosis to preserve its reparative function, rather than progressing to stiff scar formation, could mitigate fatal outcomes.

In a myocardial infarction heart failure model, Shah et al. demonstrated widespread activation of cardiac fibroblasts and upregulation of Latent TGF-β Binding Proteins (LTBPs) in fibrotic regions.4,10-12,15 Notably, LTBP2 expression was significantly elevated, a finding corroborated by studies across various heart failure and fibrosis models.4,6,10-12 These findings underscore the need to explore the poorly understood role of LTBP2 in fibrosis.

Among LTBP isoforms, LTBP2 exhibits unique interactions, with potential roles in fibrotic signaling, microfibril structural integrity, and as a biomarker for cardiac diseases. Understanding these mechanisms may reveal therapeutic targets to reduce fibrosis-related complications and improve outcomes.12

TGF-β: A Primary Activator of Myofibroblasts After Cardiac Injury

Cardiomyocytes have limited regenerative capacity, necessitating a reparative process mediated by cardiac fibroblasts that form collagen-rich scars to preserve structural integrity and prevent rupture.2,4,8 While initially adaptive, this process can progress to pathological cardiac remodeling if unregulated. The balance between tissue repair and fibrosis depends on the activation of cardiac fibroblasts.

Resident fibroblasts are typically quiescent but become activated into myofibroblasts in response to various stimuli, including mechanical stretch, pathogens, necrotic cell mediators, and inflammatory signals.3-4,7,8 Post-cardiac injury, necrotic cardiomyocytes trigger inflammatory and healing responses, altering the matrix environment via growth factors and cytokines that induce myofibroblast transdifferentiation.7

Transforming growth factor-beta (TGF-β) is a well-studied pro-fibrotic cytokine implicated in fibroblast activation.7,8,10,13 It promotes ECM production and remodeling and is highly expressed in fibrotic tissues.8,10,13,15 Macrophages are a major source of TGF-β, which is stored in the ECM in its latent form, bound to large glycoproteins called LTBPs.8,13 Activation of latent TGF-β to its active form occurs via multiple mechanisms, with small quantities inducing significant cellular responses.7 The interaction between LTBPs and TGF-β underscores the role of LTBPs as key regulators in fibrogenesis.

The LTBP Family and Its Isoforms

Latent TGF-β Binding Proteins (LTBPs) are large extracellular glycoproteins structurally similar to fibrillin microfibrils, primarily regulating TGF-β bioavailability.14,15 LTBP-1, -3, and -4 bind to the latent associated peptide (LAP) of TGF-β through disulfide bonds, with LTBP-1 and -3 binding efficiently to all three TGF-β isoforms, while LTBP-4 binds weakly to TGF-β1.13,15 LTBPs facilitate LAP folding, secretion, and deposition in the ECM, as well as TGF-β activation.14,15

TGF-β activation mechanisms include shear forces, protease activity, pH extremes, and integrin interactions via the LAP's RGD site, with integrin-mediated activation being most crucial for fibrotic diseases.14,16 Integrins bind latent TGF-β, requiring LTBP-mediated ECM incorporation and traction forces to release active TGF-β by breaking LTBP-LAP disulfide bonds.14,16 The importance of integrins was confirmed in vivo, where RGD motif mutations or integrin deletions resulted in phenotypes mimicking TGF-β1-null mice and impaired fibrosis development in hepatic, pulmonary, and renal tissues.17,18

Proteases also aid in TGF-β activation by cleaving latent complexes, while reactive conditions, such as ischemia-induced acidic environments and reactive oxygen species, contribute to activation in cardiac pathologies like myocardial infarction and ischemic cardiomyopathy.8,9,14

Loss-of-function studies highlight LTBP isoforms' developmental roles. LTBP-1 and -3 knockouts result in reduced TGF-β signaling and connective tissue abnormalities, such as cardiac septation failure in LTBP-1-null mice.15 LTBP-4 deficiency leads to abnormal lung development, cardiomyopathy, and colorectal cancer.15

Unlike other isoforms, LTBP-2 does not bind TGF-β, leaving its role in cardiac fibrosis poorly understood.

LTBP2: A Unique Member of the LTBP Family

LTBP2 is distinct among its family as it does not bind TGF-β, suggesting a unique role in cardiac fibrosis. Shah et al. identified LTBP2 as significantly upregulated in a myocardial injury heart failure model, with fold changes far exceeding other LTBP isoforms, which remained at baseline expression levels.4 This dramatic upregulation highlights LTBP2's potential importance in fibrosis and heart failure. Similarly, other studies have reported elevated LTBP2 expression in fibrotic regions across various cardiac fibrosis models.6,10,19,20

Unlike LTBP-1, -3, and -4, which regulate latent TGF-β complexes by facilitating storage, activation, and release, LTBP2 may contribute to fibrosis through alternative mechanisms such as ECM remodeling, microfibril stabilization, or interactions with other profibrotic pathways like NF-κB and FGF-2.21-24 This functional divergence could explain why LTBP2 is highly upregulated in fibrotic tissues while other isoforms remain stable. Understanding how LTBP2 influences fibrosis independently of TGF-β activation could provide novel therapeutic avenues distinct from traditional TGF-β-targeted interventions.

While in vitro studies have provided insight into LTBP2's role in fibrosis, its function in vivo remains poorly characterized. Current in vivo models, including myocardial injury-induced fibrosis and transgenic knockout studies, suggest its importance, but further research is needed to confirm whether LTBP2 directly modulates fibrosis or acts through secondary mechanisms. This review explores LTBP2's role in cardiac fibrosis, focusing on its involvement in cell signaling, microfibril integrity, and biomarker potential.

Discussion

LTBP2 AND ITS ROLE IN CARDIAC FIBROSIS SIGNALING PATHWAYS

LTBP2 plays multiple roles in the signaling pathways associated with cardiac fibrosis. Although it does not bind TGF-β directly, LTBP2 upregulates TGF-β1 expression and secretion through Akt and p38 MAPK pathways, exacerbating myofibroblast activation and fibrosis.21 This pro-fibrotic effect requires further in vivo validation, as conflicting evidence about TGF-β1 binding persists.

LTBP2 also strongly binds fibroblast growth factor-2 (FGF-2), which influences fibroblast activity. While FGF-2 promotes healing in chronic fibrosis by reducing TGF-β1-induced collagen production and inducing myofibroblast apoptosis, LTBP2 inhibits FGF-2 function, perpetuating fibrosis.22-24 Modulating this interaction could serve as a therapeutic target to enhance FGF-2's anti-fibrotic effects.

Additionally, LTBP2 influences fibroblast apoptosis via caspase-3 activation. Shi et al. showed that ISO-treated cardiac fibroblasts with elevated LTBP2 levels experienced increased apoptosis.6 However, it remains unclear if this apoptosis is selective for reparative or myofibroblasts, a key distinction that requires further research.25

Pang et al. demonstrated that LTBP2 knockdown in a rat dilated cardiomyopathy model reduced fibrosis, oxidative stress, and inflammation via NF-κB signaling suppression.20 Similarly, in pulmonary fibrosis models, LTBP2 silencing reduced fibroblast-to-myofibroblast differentiation by attenuating NF-κB activation, both with and without TGF-β1 involvement.26 These findings suggest that LTBP2-targeted therapies, particularly through NF-κB inhibition, may mitigate fibrosis progression.

LTBP2 AND THE STRUCTURAL INTEGRITY OF MICROFIBRILS

LTBP2 plays a critical role in maintaining extracellular matrix (ECM) microfibril integrity, especially in elastic tissues. It serves as a bridging component of 10-nm microfibrils, structures present in various organs including the heart. While LTBP2's function is well-characterized in ocular and pulmonary tissues, its contribution to cardiac fibrosis remains underexplored.

In the eye, LTBP2 is essential for proper microfibril assembly and lens development. LTBP2-null mice exhibit disorganized microfibrils and phenotypic defects that can be rescued with recombinant LTBP2.27 Additionally, LTBP2 deficiency disrupts ciliary zonule formation, further supporting its structural role.27 Mutations in LTBP2 are also associated with primary congenital glaucoma due to trabecular meshwork malformation, raising the possibility that similar ECM defects could contribute to fibrosis in other organs, including the heart.28–29

LTBP2 also interacts with fibulin-5 (DANCE), a protein critical for elastogenesis. By regulating DANCE's binding to fibrillin-1 microfibrils, LTBP2 promotes elastic fiber deposition.30 This interaction may be relevant in the cardiac ECM, where elastic fiber remodeling is a key component of fibrosis.

In summary, LTBP2 is vital for ECM microfibril organization and elastic fiber formation. While evidence from ocular models suggests a structural role, further studies in cardiac tissues are needed to elucidate its contribution to fibrosis progression and scar stabilization in heart disease.

LTBP2 AS A POTENTIAL BIOMARKER FOR EARLY-STAGE FIBROSIS

LTBP2 has emerged as a promising biomarker for early-stage fibrosis across various organ systems. In pulmonary fibrosis, serum levels of LTBP2 have been shown to correlate with the differentiation of lung fibroblasts to myofibroblasts, especially following TGF-β1 induction.11 A study using the Cox hazard model found that serum LTBP2 levels could predict the prognosis of idiopathic pulmonary fibrosis.11 Furthermore, LTBP2 overexpression in bleomycin-induced pulmonary fibrosis models also led to myofibroblast differentiation via NF-κB signaling, even in the absence of TGF-β1.26 Notably, serum LTBP2 levels were elevated in COVID-19-related pulmonary fibrosis, suggesting its potential as a biomarker for fibrotic diseases.

While these findings are promising in pulmonary fibrosis, further research is needed to explore LTBP2's biomarker potential in cardiac fibrosis. In the context of cardiac fibrosis, LTBP2 is highly upregulated in fibrotic regions and secreted into the ECM. A 2018 study by Park et al. observed higher LTBP2 levels in isoproterenol-induced hypertrophic cardiomyopathy mice.10 However, they did not find significant differences in serum LTBP2 levels between heart failure patients and healthy controls. A follow-up study did show elevated serum LTBP2 in heart failure patients with reduced

ejection fraction, but the protein's localization to fibrotic regions and its expression in various types of fibrosis limited its effectiveness as a circulating biomarker.12,19

Future research should focus on developing more sensitive assays, such as using coronary sinus blood samples (which contain the highest concentration of LTBP2), and improving antibody specificity to enhance LTBP2's potential as a biomarker for cardiac fibrosis and heart failure.

Future Directions

Most of our current understanding of LTBP2 cell signaling in cardiac fibrosis originates from in vitro tests using isolated fibroblasts modeling fibrosis. However, these models fail to capture the full complexity of cardiac fibrosis, which involves dynamic interactions between fibroblasts, myocytes, immune cells, and extracellular matrix components. More in vivo studies are needed to clarify LTBP2's role in fibrosis progression and cardiac remodeling.

In addition to its use as a biomarker, LTBP2 holds potential as a therapeutic target for cardiac fibrosis. Given its involvement in key fibrosis-related signaling pathways such as NF-κB, TGF-β1, and microfibril integrity, targeting these pathways could provide a dual strategy in modulating LTBP2 expression. 6,20-26 For instance, downregulating NF-κB signaling reduced cardiac fibrosis in DCM rats, highlighting its potential as a target.20

Therapeutic interventions may include the use of small molecules or monoclonal antibodies to either inhibit LTBP2's pro-fibrotic effects or regulate its interactions with ECM components.26-30 Targeting receptors involved in LTBP2 signaling, such as integrins or proteases, could enable more precise interventions while minimizing off-target effects.27-30 Furthermore, viral gene delivery systems, such as adeno-associated viral vectors, could be explored for selective modulation of LTBP2 expression in cardiac tissue to promote reparative fibrosis.28

Future studies should refine these strategies using preclinical models to identify the most effective approaches. A deeper understanding of LTBP2 in cardiac fibrosis will be essential for developing targeted therapies to prevent heart failure and improve patient outcomes.

Study Limitations

While many cited studies provide valuable insights, most are limited to in vitro systems or animal models that may not fully replicate human cardiac fibrosis. The translational relevance of these findings remains uncertain, underscoring the need for more robust in vivo and clinical studies to validate LTBP2's role and therapeutic potential in humans.

Search Methods

A narrative literature review was conducted using the University of Toronto library databases. Keyword combinations such as "LTBP2," "fibrosis," and "ECM" were used. Articles were selected based on abstract relevance and peer-reviewed primary research, focusing on studies exploring LTBP2's role in fibrosis.

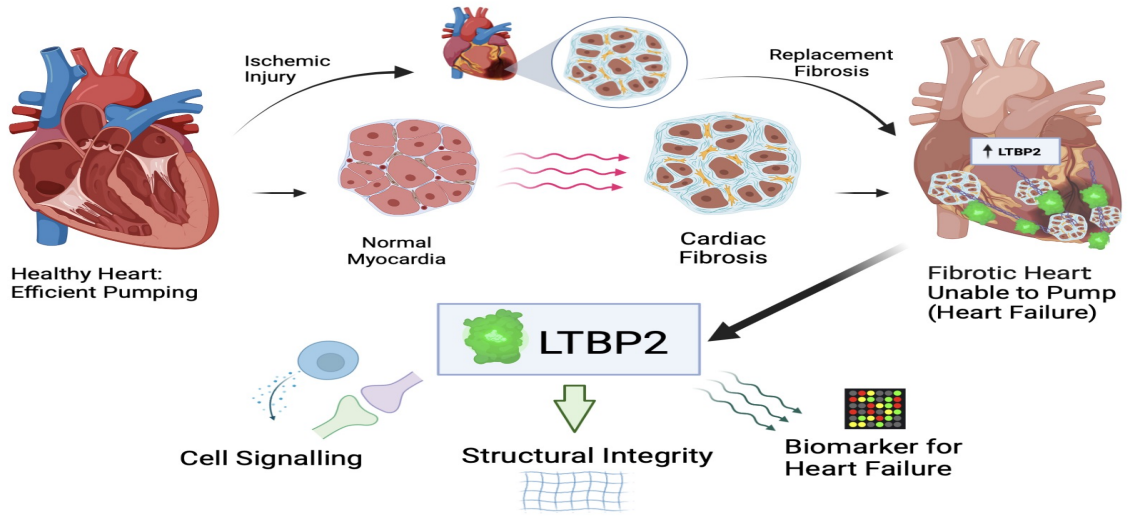


Figure 1. Progression of Cardiac Fibrosis and Potential Functions of LTBP2 31

LTBP2 is upregulated in cardiac fibrosis and may contribute to fibrosis progression through involvement in key cell signaling pathways and maintenance of microfibril integrity. Additionally, its early upregulation in fibrotic tissue and detection in serum suggest its potential as a biomarker for early-stage cardiac fibrosis.

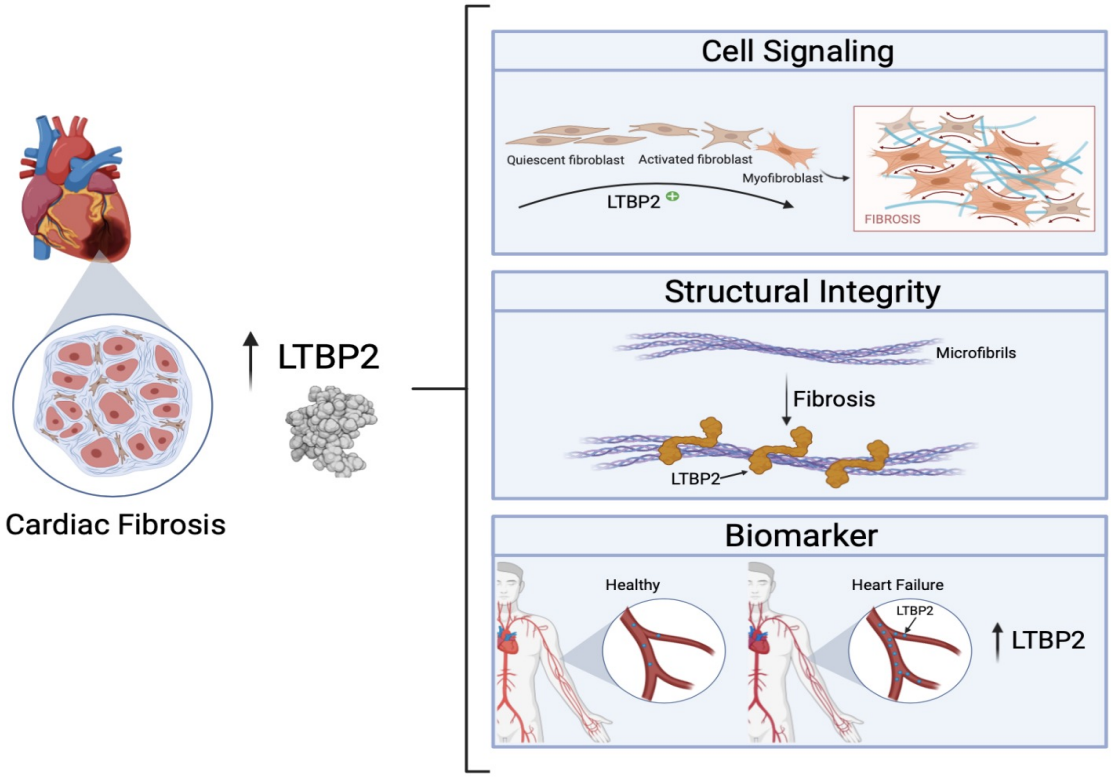


Figure 2. LTBP2 as a Tool for Understanding and Treating Cardiac Fibrosis 31

Exploring the role of LTBP2 in cardiac fibrosis through its involvement in cell signaling pathways, maintenance of microfibril integrity, and potential as a biomarker for early fibrosis and heart failure.

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