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Review

Advances in the Role of Versican in Cardiac Remodeling

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Abstract

Cardiac remodeling, the core pathological process underlying various cardiovascular diseases such as myocardial infarction, hypertensive heart disease, and heart failure, involves cardiomyocyte hypertrophy, apoptosis, fibrosis, and dynamic remodeling of the extracellular matrix (ECM), all of which seriously impair cardiac function and affect patient prognosis. Versican is a key ECM proteoglycan that plays an essential role in regulating cell adhesion, migration, proliferation, and inflammatory responses. Abnormal versican expression has been implicated in pathological cardiac remodeling. This review summarizes the molecular structure, major isoforms, and spatiotemporal expression patterns of versican in both normal and pathological cardiac remodeling. Specifically, this review focuses on the mechanisms through which versican mediates cardiac remodeling, including the regulation of inflammatory cell recruitment, fibroblast activation, myocardial fibrosis, and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-mediated proteolysis, as well as the role versican plays in the pathological processes underlying cardiac remodeling in different cardiovascular diseases. We further discuss stage-specific therapeutic strategies targeting versican, with an emphasis on biomarker-guided timing, fibroblast-selective delivery, isoform-specific intervention, and unresolved translational challenges.

Keywords: versican; cardiomyocytes; cardiac remodeling; extracellular matrix; proteoglycans; fibrosis; heart failure; ADAMTS proteins

1. Introduction

Cardiac remodeling refers to the structural, functional, and genetic expression changes that occur in the heart in response to pathological stimuli, such as hemodynamic overload, ischemic injury, metabolic disturbance, or excessive activation of neurohumoral factors. This is the core link between heart failure occurrence and development [1,2]. This process involves complex interactions between cardiomyocytes and non-cardiomyocytes (e.g., fibroblasts, immune cells), accompanied by profound extracellular matrix (ECM) remodeling [3,4]. Metabolic remodeling, a key driver of heart failure and an important component of cardiac remodeling, is characterized by disordered substrate utilization, impaired mitochondrial oxidative metabolism, reduced glucose oxidation, glycolysis uncoupling from glucose oxidation, insufficient adenosine triphosphate production, and increased oxidative stress [5]. The ECM provides physical support for cardiomyocytes and actively participates in signal transduction by storing and releasing growth factors and regulating cellular behavior [2,4]. Versican is a chondroitin sulfate chain-rich proteoglycan in the ECM that belongs to the aggrecan family [6,7]. Versican expression is relatively low in the normal adult myocardium, but it is reactivated during myocardial injury, pressure overload, and fibrotic matrix remodeling [8,9]. Accumulating evidence indicates that versican plays a dual role in remodeling processes such as post–myocardial infarction (MI) repair, pressure overload–induced myocardial hypertrophy, and fibrosis [8,9]. On the one hand, it serves as a "scaffold" for inflammatory cell infiltration; on the other hand, it is a key regulatory factor in fibroblast activation and collagen deposition [10,11,12].

Despite increasing interest in elucidating versican biology, a mechanistic understanding of how distinct versican isoforms regulate cardiac remodeling remains incomplete. Versican-directed interventions have shown experimental promise but remain at an early preclinical stage. Here we summarize the current evidence of versican structure, isoform dynamics, regulatory mechanisms, and therapeutic implications in cardiac remodeling and pay particular attention to the unresolved questions that limit clinical translation. Although versican primarily acts within the ECM and non-cardiomyocyte compartments, its effects on matrix mechanics, inflammatory signaling, and fibroblast behavior can indirectly influence cardiomyocyte hypertrophy, survival, and proliferation as well as ventricular function. Recent experimental evidence has consistently shown that fibrotic ECM can activate mechanosensitive pathways and alter the cardiomyocyte phenotype and function, supporting the concept that ECM remodeling is a direct regulator of cardiomyocyte behavior [13].

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Table 1. Structural characteristics and biological functions of major versican isoforms.

Isoform	Domain Composition	Relative GAG Content	Expression Profile	Key Biological Functions	References
V0	G1-CSα-CSβ-G3	Most abundant	Embryonic development and early myocardial injury	Contributes to cardiovascular development; alterations in versican isoform expression are associated with changes in cardiac morphology.	[18,19]
V1	G1-CSβ-G3	Moderate	Pathological conditions	Associated with fibroblast activation, ECM expansion, and pathological remodeling.	[8,9,20]
V2	G1-CSα-G3	Moderate	Detected in selected adult cardiac regions; predominance in normal adult myocardium remains uncertain	Forms HA-associated matrix complexes; may contribute to matrix organization and biomechanical stability.	[20]
V3	G1-G3 (lacks all GAG domains)	Minimal/ none (smallest molecular weight)	Tissue/stage-specific	May suppress cell proliferation and modulate extracellular matrix accumulation in certain experimental models; its role in cardiac remodeling remains to be established.	[21]

ECM, extracellular matrix; GAG, glycosaminoglycan; HA, hyaluronan.

2. Versican Structure, Isoforms, and Spatiotemporal Expression in the Heart

2.1 Molecular Structure and Functional Domains of Versican

Versican is a large chondroitin sulfate proteoglycan encoded by the *VCAN* gene, with a core protein molecular weight of 400–600 kDa. Fully glycosylated holoproteins can exceed 1000 kDa. Its structural diversity is derived from the alternative splicing of precursor mRNA and post-translational modifications of the protein core [6]. The protein core contains three major domains: the N-terminal G1 domain, the central glycosaminoglycan (GAG) attachment domain, and the C-terminal G3 domain. Among them, the GAG attachment domains are the main sites for binding the chondroitin sulfate and dermatan sulfate side chains, and the number and type of GAG side chains directly affect the biological function of versican [14]. Based on alternative splicing of its two GAG attachment domains, the *VCAN* gene can be transcribed into four major splicing isoforms: V0, V1, V2, and V3. Each isoform exhibits distinct structural characteristics and functional biases due to domain composition differences [15,16,17] (Table 1, Ref. [8,9,18,19,20,21]). Different splicing isoforms exhibit tissue- and stage-specific expression, and their structural differences determine the diversity of binding partners and biological functions that also serve as the structural basis for versican to regulate multiple biological processes.

2.2 Versican Expression in Normal Adult and Developing Heart

Versican is expressed at relatively low levels in the normal adult cardiac ECM. Although exon 7–containing isoforms, corresponding to V0 and/or V2, have been detected in specific adult cardiac regions, the precise isoform distribution in the normal adult myocardium remains incompletely defined; therefore, current evidence is insufficient to conclude that V2 predominates in the normal adult heart [9,19]. Versican interacts with hyaluronan (HA) through its N-terminal G1 domain to form large proteoglycan–HA complexes that contribute to matrix hydration, organization, and biomechanical stability [6,22]. During embryogenesis, versican–HA-rich matrices are essential for endocardial cushion formation, valve morphogenesis, and chamber maturation [19,23]. Genetic studies further support the essential role of versican in cardiovascular development, as versican deficiency can cause severe cardiac malformations and embryonic lethality, whereas altered versican isoform expression is associated with abnormalities in cardiac morphology [18,19,23]. In contrast, in the adult myocardium, versican-containing HA-rich matrices should be considered interstitial or pericellular ECM components rather than as cardiac jelly [22].

2.3 Disease- and Stage-Dependent Versican Expression in Cardiac Remodeling

Under pathological stimuli that induce cardiac remodeling, the expression level, splice isoform composition, and spatial distribution of versican undergo disease-, stage-, and region-dependent changes [9]. These dynamic expression patterns provide an important descriptive basis for understanding the context-dependent roles of versican in cardiac remodeling, and the underlying mechanisms are discussed separately in the following sections [8,9].

Versican is rapidly induced in infarcted and border-zone myocardium during the early inflammatory phase of MI. In a rat MI model, versican mRNA was upregulated as early as 6 h post-infarction, peaked at approximately 2 days, and then gradually declined during scar maturation [24,25]. This transient increase is mainly associated with monocytes/macrophages infiltration into the infarcted region, indicating that versican expression is closely linked to early post-infarction inflammatory and provisional matrix response [26]. A recent spatial multiomics analysis of human MI showed that post-infarction remodeling is spatially organized into distinct injury, repair, and remodeling zones with coordinated immune, fibroblast, and ECM programs [27]. The functional consequences of macrophage-derived versican are discussed in Section 3.1.

Versican expression also increases during pressure overload and hypertensive cardiomyopathy, with V0 and V1 being the major isoforms detected during fibrosis development [9]. Versican first accumulates in the perivascular regions and subsequently extends into the myocardial interstitium, a spatial pattern that parallels the progression of myocardial fibrosis [9]. Notably, V1 expression appears early in collagen-producing fibroblasts before overt collagen accumulation, suggesting that versican may be an early marker of fibrotic matrix remodeling [9].

The potential involvement of versican in heart failure with preserved ejection fraction (HFpEF) remains poorly defined. HFpEF is characterized by diastolic dysfunction, increased myocardial stiffness, and prominent ECM remodeling [9]. A recent single-cell transcriptomic analysis in a high-fat diet plus *N*ω-nitro-L-arginine methyl ester–induced HFpEF mouse model showed fibroblast and macrophage activation together with perivascular fibrosis and increased basement membrane components such as collagen IV [28]. Given the perivascular accumulation of versican observed during pressure overload–induced fibrosis, these findings provide an indirect rationale for investigating versican in HFpEF-associated matrix remodeling [9,28]. However, direct evidence of expression, isoform composition, and function in the myocardium of patients with HFpEF remains limited.

Increased versican expression is also associated with myocardial fibrosis in human cardiomyopathies. In hypertrophic and dilated cardiomyopathies, versican and versican fragments containing the DPEAAE neoepitope accumulate in fibrotic regions and correlate with collagen expression [9]. A proteomic analysis of the human left ventricular myocardium consistently identified *VCAN* as a significantly upregulated ECM protein in dilated cardiomyopathy compared to that in donor hearts [29]. However, direct evidence demonstrating a consistent V0/V1 increase and V2 decrease in human dilated or hypertrophic cardiomyopathy remains limited; therefore, disease-specific isoform shifts in human cardiomyopathy require further investigation.

Taken together, these findings indicate that versican expression during cardiac remodeling is highly context-dependent and varies by disease type, remodeling stage, anatomical region, cellular source, and isoform composition. These descriptive expression patterns provide the basis for mechanistic discussion in the following sections and are summarized in Fig. 1.

3. Core Mechanisms of Versican in Regulating Cardiac Remodeling

3.1 Versican in Inflammatory Cell Recruitment and Macrophage Responses

3.1.1 Versican-Rich Provisional Matrix and Inflammatory Cell Recruitment

After myocardial injury, versican contributes to the formation of a provisional ECM that facilitates inflammatory cell recruitment and retention. Versican can bind to and retain chemokines within the injured matrix through its chondroitin sulfate chains, thereby supporting local chemokine gradients and promoting the recruitment of inflammatory cells, particularly monocytes/macrophages [10]. Versican also interacts with HA, tumor necrosis factor–stimulated gene-6, and inter-α-inhibitor to form a stabilized HA-rich matrix scaffold. This scaffold may function as a permissive “landing zone” for inflammatory cells to enter injured tissues [10,30].

3.1.2 Context-Dependent Regulation of Macrophage Activation by Versican and Its Fragments

In addition to supporting inflammatory cell recruitment, versican may influence macrophage activation and polarization after MI. These effects are likely dependent on its molecular form, including full-length versican, splice variants, and proteolytic fragments, as well as the local inflammatory and ECM microenvironments [10,11]. Therefore, versican should not be believed to act through a single uniform mechanism but rather as a context-dependent modulator of macrophage behavior.

During the acute inflammatory phase, versican proteolytic fragments, including versikines, may act as immunomodulatory matrix–derived signals; however, whether they function as classical damage-associated molecular patterns in the infarcted myocardium remains to be elucidated. Versican has been reported to modulate macrophage-related inflammatory signaling, particularly through TLR2–MyD88-dependent pathways, in inflammatory and ECM remodeling contexts [10,11]. However, the extent to which this mechanism operates directly in the infarcted myocardium remains unclear. Therefore, current evidence should be interpreted in a tiered manner: direct cardiac evidence supports versican upregulation in infiltrating macrophages after MI, whereas several receptor-mediated mechanisms of versican fragments have been inferred from non-cardiac inflammatory models and require validation in infarcted myocardium [10,11,24,25,31].

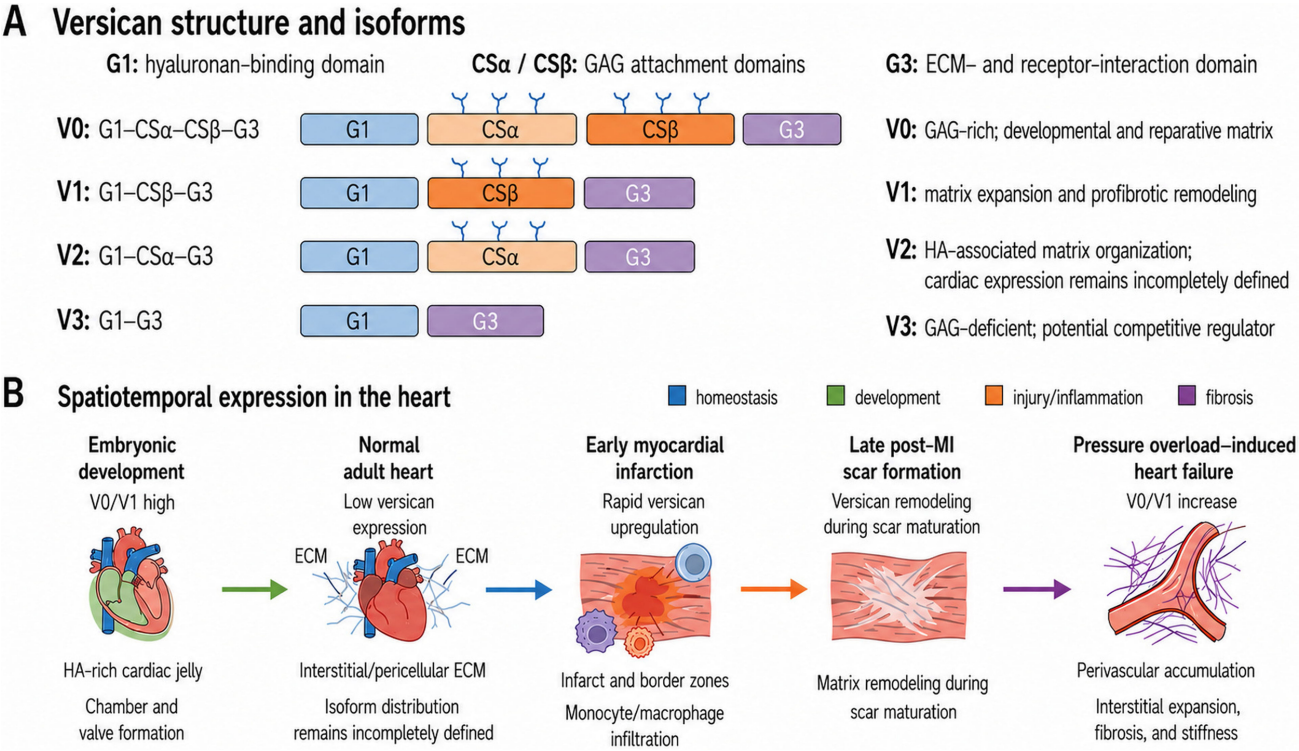


Fig. 1. Versican domain organization, splice isoforms, and spatiotemporal expression during cardiac remodeling. (A) Schematic representation of versican domain organization and major splice isoforms. Full-length versican contains an N-terminal G1 domain, central CSα and/or CSβ glycosaminoglycan attachment regions, and a C-terminal G3 domain. Alternative splicing generates V0, V1, V2, and V3 isoforms, which differ in the presence or absence of CSα and CSβ domains. (B) Overview of reported versican expression patterns across cardiac development and remodeling processes. Versican is abundant during embryonic cardiac development, expressed at low levels in the normal adult heart, rapidly upregulated after myocardial injury, and associated with matrix remodeling during post-infarction scar formation and pressure overload–induced heart failure. CS, chondroitin sulfate; ECM, extracellular matrix; GAG, glycosaminoglycan; HA, hyaluronan; MI, myocardial infarction. Note: This figure is an original schematic created by the authors using generative AI tools. No copyrighted images were reproduced.

The immunomodulatory effects of versican appear to be isoform- and modification-dependent. For example, in lipopolysaccharide-induced inflammatory models, reduced V1 expression is associated with activation of the specificity protein 1–TLR2–NF-κB axis and amplification of the inflammatory responses [32]. In addition, oxidative stress products such as peroxynitrite can modify V3 isoform structure and function, potentially altering its interactions with ECM components and cellular receptors [30]. These findings suggest that the inflammatory effects of versican are influenced by its isoform composition, proteolytic processing, post-translational modifications, and tissue context. Nevertheless, these mechanisms have not been fully validated in cardiac injury models and should be interpreted as potential rather than definitive mechanisms of post-infarction inflammation.

It should also be noted that cytokines such as interleukin (IL)-1β, tumor necrosis factor–α, and IL-6 largely reflect the broader post-infarction inflammatory milieu rather than versican-specific downstream effectors [33,34,35]. Excessive or persistent production of these cytokines can contribute to cardiomyocyte injury, fibroblast activation, ECM remodeling, and adverse ventricular remodeling [36]. Recent evidence further indicates that IL-1β-dependent communication between $CCR2^{+}$ monocytes/macrophages and fibroblasts promotes profibrotic fibroblast states, myocardial fibrosis, and cardiac dysfunction in heart failure [37]. Thus, versican may indirectly influence cardiac remodeling by regulating macrophage recruitment and activation within this cytokine-rich inflammatory environment rather than by uniquely controlling these cytokine pathways.

3.1.3 Remaining Questions and Therapeutic Implications

Several critical questions regarding the relationship between versican and macrophage responses in cardiac remodeling remain unresolved. First, it is unclear whether versican directly induces macrophage polarization through receptor-mediated signaling or indirectly influences macrophage phenotypes by remodeling the inflammatory ECM microenvironment. Second, the spatiotemporal distribution and functional divergence of full-length

versican, splice variants, and proteolytic fragments after MI remain insufficiently defined. Third, definitive causal evidence is required to determine whether full-length versican exerts pro-reparative effects and versikines have distinct immunomodulatory functions in infarcted hearts. Finally, the optimal therapeutic window for versican-associated inflammation remains unknown. Future studies integrating spatial transcriptomics, proteomics, and cell-specific loss- or gain-of-function approaches may help to clarify how different versican forms regulate post-infarction inflammation and remodeling. Such evidence is essential for evaluating whether versican represents a viable therapeutic target for modulating macrophage responses, limiting excessive inflammation, and improving ventricular remodeling after MI.

3.2 Versican in Fibroblast Activation and Profibrotic Matrix Remodeling

3.2.1 Versican as Early Matrix Organizer in Cardiac Fibrosis

Myocardial fibrosis, a core pathological feature of cardiac remodeling, is characterized by excessive deposition of types I and III collagen and increased ECM cross-linking [3,38]. Excessive activation and proliferation of cardiac fibroblasts, together with their transition into collagen-secreting myofibroblasts, contributes to pathological remodeling, heart failure, and arrhythmias [39,40]. During this process, versican, particularly the V1 isoform, appears to occupy an early position within the fibrotic cascade [17]. Under pathological stimuli such as pressure overload, versican expression is rapidly upregulated and its protein deposition extended from the perivascular region into the myocardial interstitium before overt collagen accumulation, supporting the concept that versican acts as an early ECM organizer in cardiac fibrosis [9]. Thus, versican may not simply be a passive ECM component but may help coordinate fibroblast activation and matrix remodeling through signaling and mechanosensitive regulation.

3.2.2 Transforming Growth Factor–β/Smad-Dependent VCAN Transcription and Mechanosensitive Feedback

Versican expression in cardiac fibroblasts is regulated by several signaling pathways rather than a single upstream stimulus [17]. Oncostatin M, a cytokine of the IL-6 family, can increase versican expression through glycoprotein 130/Janus kinase/signal transducer and activator of transcription 3 signaling, thereby linking inflammatory stimulation with ECM remodeling [12,41]. Transforming growth factor–β (TGF-β)/Smad signaling is another central pathway involved in *VCAN* transcriptional regulation.

After TGF-β receptor activation, phosphorylated Smad2/3 associates with Smad4 and translocates to the nucleus, where Smad complexes regulate target gene transcription through Smad-binding elements (SBEs). The canonical SBE sequence is 5′-GTCT-3′, or the complementary 5′-AGAC-3′ sequence, within regulatory regions of TGF-β-responsive genes [42]. In the context of *VCAN* regulation, evidence from knockdown and deletion studies supports the role of Smad-dependent transcriptional control. Smad2 knockdown reduces the expressions of versican, fibronectin, and periostin in unstimulated cardiac myofibroblasts, whereas fibroblast-specific Smad2/3 deletion suppresses the expressions of ECM genes, including versican, and attenuates pressure overload–induced fibrosis in mice [43,44]. These data support the role of TGF-β/Smad2/3 signaling in regulating versican expression, although the exact Smad-occupied *VCAN* promoter or enhancer regions in cardiac fibroblasts remain to be defined [42,43,44,45,46]. This pathway may also be reinforced by mechanical feedback from the remodeled ECM. As versican accumulates along with other fibrotic matrix components, the pericellular matrix expands and the myocardium stiffens. Increased matrix stiffness enhances the mechanical loading on activated fibroblasts and promotes integrin-dependent mechanotransduction.

Integrins αvβ3 and αvβ5, which are upregulated on differentiated cardiac myofibroblasts, can bind the Arg-Gly-Asp motif within the latency-associated peptide (LAP) of ECM-tethered latent TGF-β1 complexes. Under increased matrix tension, integrin-transmitted traction forces induce conformational changes in LAP, thereby releasing biologically active TGF-β1 [47]. This mechanism has been directly demonstrated in human cardiac fibroblasts, wherein αvβ3 and αvβ5 independently drive latent TGF-β1 activation and myofibroblast differentiation, with simultaneous blockade of both integrins abolishing contractility-driven TGF-β1 release [48]. The released active TGF-β1 can then bind TGF-β receptors I and II on fibroblasts, increasing receptor kinase activity and Smad2/3 phosphorylation. This provides a plausible feedback route by which a versican-enriched and stiffened ECM further enhances TGF-β signaling: versican deposition → ECM expansion and stiffening → integrin-mediated latent TGF-β1 activation → TGF-β receptor activation → Smad2/3 signaling → further *VCAN* transcription. This loop may contribute to the progressive and self-sustaining nature of myocardial fibrosis.

3.2.3 Crosstalk with CTGF/CCN2 and Platelet-Derived Growth Factor Signaling

Versican-mediated matrix remodeling intersects with other established profibrotic mediators, particularly connective tissue growth factor/cellular communication network factor 2 (CTGF/CCN2) and platelet-derived growth factors (PDGF). CTGF/CCN2, a well-recognized downstream effector of TGF-β signaling, can act in an autocrine manner in cardiac fibroblasts. In this context, CTGF/CCN2 promotes both versican and collagen deposition, thereby reinforcing fibroblast-dependent ECM accumulation and fibrotic remodeling [49,50]. The fibroblast-

specific deletion of CTGF/CCN2 consistently abolishes the angiotensin II–induced fibrotic response in mice, whereas the cardiomyocyte-specific deletion does not produce the same antifibrotic effect [49,50]. PDGF, acting through PDGF receptor–β, regulates versican through two mechanistically distinct but cooperative intracellular pathways. ERK signaling selectively promotes versican core protein mRNA transcription, whereas protein kinase C signaling enhances glycosaminoglycan chain elongation of the versican core protein [51,52,53].

Together, these effects expand the pericellular matrix and facilitate fibroblast proliferation, migration, and ECM remodeling. Therefore, versican should not be considered an isolated ECM component; rather, it appears to function as a matrix-associated effector within the broader TGF-β–CTGF/CCN2–PDGF profibrotic signaling networks.

3.2.4 Isoform-Specific Regulation of Myofibroblast Proliferation and Survival

Although direct evidence in cardiac fibroblasts remains limited, studies of non–cardiac cell systems suggested that versican isoforms differentially regulate cell proliferation and survival. The V1 isoform activates the epidermal growth factor receptor (EGFR) and downstream signaling, leading to proteasomal degradation of the cyclin-dependent kinase inhibitor $p27^{Kip1}$. This enhances cyclin-dependent kinase 2 activity and promotes G1-to-S phase cell-cycle progression. V1 also downregulates the pro-apoptotic protein Bad, thereby protecting activated myofibroblasts against apoptosis [20]. In contrast, the V2 isoform suppresses EGFR expression, inhibits fibroblast proliferation, and provides limited apoptotic resistance. This functional divergence suggests that V1 predominance in the fibrotic myocardium favors the persistence of apoptosis-resistant myofibroblasts and contributes to sustained pathological fibrosis.

3.3 A Disintegrin and Metalloproteinase With Thrombospondin Motifs–Mediated Versican Proteolysis in Cardiac Matrix Remodeling

3.3.1 Structural Basis of a Disintegrin and Metalloproteinase With Thrombospondin Motifs–Mediated Versican Cleavage

The proteolysis of versican mediated by a disintegrin and Metalloproteinase with Thrombospondin motifs (ADAMTS) participates in normal cardiovascular development and plays an important regulatory role in cardiac matrix remodeling under pathological conditions [54,55,56]. Members of the ADAMTS family contain a conserved N-terminal catalytic metalloproteinase domain with the canonical Zn^{2+}-binding motif HEXXHXXGXXH, which is responsible for peptide bond hydrolysis. The principal ADAMTS cleavage site in versican is located within the GAG-β domain at the Glu^{441}–Ala^{442} bond. Cleavage at this site generates an N-terminal bioactive fragment, termed versikine, along with a C-terminal residual fragment. The DPEAAE neoepitope exposed at the C-terminus of versikine is commonly used as a marker of ADAMTS-mediated versican proteolysis *in vivo* [57,58]. Among the ADAMTS proteases, ADAMTS1, ADAMTS4, and ADAMTS5 are the principal enzymes with versicanase activity. ADAMTS5 generally shows the highest catalytic efficiency toward versican, followed by ADAMTS4, whereas ADAMTS1 has weaker intrinsic versicanase activity under comparable *in vitro* conditions [59,60]. Importantly, the substrate selectivity is not determined by the catalytic domain alone. Instead, efficient versican cleavage depends on exosite-mediated substrate recognition within the ancillary domains, particularly the spacer domain. Hypervariable loops in the spacer domain are critical for versican binding, and their disruption markedly reduces versicanase activity. In ADAMTS5, the cysteine-rich domain contributes to substrate engagement and positioning, thereby supporting a multidomain model of substrate recognition [59].

3.3.2 Cell Type–Specific ADAMTS Expression and Local Versican Turnover

ADAMTS expression shows marked cell-type specificity in the heart. ADAMTS5 is highly expressed in cardiac fibroblasts and an important protease within the fibroblast secretome, suggesting a major role in proteoglycan-rich interstitial matrix remodeling. In contrast, ADAMTS1 is more closely associated with vascular cell populations, including endothelial cells, pericytes, and smooth muscle cells, indicating its potential role in perivascular matrix remodeling. ADAMTS4 also appears to be enriched in pericytes and smooth muscle cells but not interstitial fibroblasts. This compartmentalized expression pattern suggests that ADAMTS5 primarily regulates fibroblast-associated interstitial versican turnover, whereas ADAMTS1 contributes to vascular or perivascular remodeling responses [26].

3.3.3 TIMP3–ADAMTS Balance in Versican Homeostasis and Heart Failure

ADAMTS-mediated versican proteolysis is regulated by the tissue inhibitors of metalloproteinases (TIMPs). Among the four TIMP members, TIMP3 is the most relevant endogenous inhibitor of ADAMTS versicanases because it effectively inhibits ADAMTS1, ADAMTS4, and ADAMTS5, whereas TIMP1 and TIMP2 bind to the ECM. This ECM-binding property enables TIMP3 to localize near versican-rich pericellular matrices and directly inhibit ADAMTS-dependent versican cleavage.

In a failing heart, disruption of TIMP3–ADAMTS balance may impair orderly versican turnover. Reduced TIMP3 expression and altered ADAMTS5-dependent versican processing are associated with intact versican accumulation, reduced versikine generation, and proteoglycan-rich matrix remodeling disorganization. Thus, the TIMP3–ADAMTS5 axis may be a local regulatory checkpoint for

myocardial versican homeostasis and represents a potential therapeutic target for restoring ECM balance during cardiac remodeling.

Together with the structural specificity and cell type–specific expression of ADAMTS proteases described above, genetic and pharmacological studies have provided direct evidence that the ADAMTS–versican axis actively contributes to proteoglycan-rich matrix remodeling and cardiac dysfunction. In a heart failure model, catalytic ADAMTS5 inactivation led to pronounced accumulation of intact versican, loss of ADAMTS-derived versikine, disruption of the HA-rich matrix, and impaired left ventricular function after angiotensin II challenge. Importantly, these abnormalities occurred without parallel increases in collagen deposition or inflammatory cell infiltration, indicating that proteoglycan remodeling may represent a distinct pathological component of cardiac remodeling rather than a secondary consequence of collagen fibrosis [26].

3.3.4 Developmental and Profibrotic Consequences of Dysregulated ADAMTS Activity

Developmental studies have supported the importance of regulating versican proteolysis. During embryogenesis, genetic or pharmacological disruption of ADAMTS-dependent versican processing results in excessive accumulation of versican-rich cardiac jelly and impaired formation of compact trabecular myocardium [56,61]. These findings suggest that timely versican clearance is essential for cardiac development and matrix organization maintenance under pathological stress. Related ADAMTS proteases may also contribute to adverse cardiac remodeling through additional matrix-dependent mechanisms. In pressure-overload models, the pharmacological inhibition of ADAMTS4 attenuates myocardial fibrosis and functional deterioration, at least in part by limiting proteolytic release of ECM-bound latent TGF-β from substrates such as latent TGF-β-binding protein 1 and extra domain A–fibronectin [62]. Although this mechanism is not limited to versican cleavage, it highlights the broader capacity of ADAMTS proteases to remodel profibrotic ECM signaling niches. Thus, ADAMTS-mediated matrix proteolysis should be viewed not merely as a marker of ECM turnover but as an active regulatory mechanism that shapes myocardial structure and mechanics as well as fibrotic signaling. Collectively, versican participates in cardiac remodeling through the coordinated regulation of inflammatory cell recruitment, macrophage activation, fibroblast-driven matrix remodeling, and ADAMTS-dependent proteolytic turnover. The mechanisms and their therapeutic implications are summarized in Fig. 2.

4. Therapeutic Targeting of Versican in Cardiac Remodeling: Stage Specificity and Translational Challenges

Recent experimental evidence suggests that versican promotes cardiomyocyte proliferation and cardiac repair in specific regenerative or injury contexts [8]. Together with its established role in ECM remodeling, this finding highlights the functional duality of versican: early reparative versus late pathological. This duality defines the therapeutic potential and is a key constraint in interventional design. Although early versican activity may support reparative matrix organization and cardiac repair, persistent V1-enriched accumulation may promote fibrotic and adverse ventricular remodeling. Therefore, versican-directed therapy should be stage-specific rather than broadly inhibitory. However, the precise isoform, dosage, timing, and delivery strategy required to harness its benefits while avoiding maladaptive fibrotic signaling remain undefined.

4.1 Defining Therapeutic Window Using Versican-Derived Biomarkers

Temporal precision is a central challenge in versican-directed therapy. In murine models of pressure overload, V1 expression increases early and persists, whereas ADAMTS-generated DPEAAE versican fragments predominantly accumulate during late fibrosis [9]. This temporal dissociation supports the myocardial DPEAAE to full-length versican ratio as a candidate marker for transition from reparative to pathological remodeling. Circulating versican neoepitopes may also provide translational clues. Plasma levels of the VCANM matrix metalloproteinase 12–derived versican fragment are elevated in coronary artery disease and acute coronary syndrome, suggesting that versican proteolytic signatures may reflect disease activity *in vivo* [63]. Similarly, assays targeting ADAMTS-derived versican fragments may have potential utility in monitoring post-infarction matrix remodeling and informing the timing of therapeutic interventions, although further clinical validation is required. However, these candidate biomarkers require validation in longitudinal cardiac cohorts and correlation with imaging-based measures of fibrosis, ventricular function, and clinical outcomes.

4.2 Cardiac Fibroblast–Targeted Delivery and Gene-Silencing Strategies

However, delivery remains a major barrier to versican-directed therapy. Its systemic administration is limited by poor retention in the infarcted myocardium and predominant hepatic uptake. ECM-integrated lipid nanoparticles reportedly improve cardiac retention and fibroblast uptake in experimental models; however, efficient cell-specific targeting in injured human hearts remains unresolved [64]. Gene-silencing strategies, including small interfering RNA, short hairpin RNA, and clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9–based approaches, are conceptually attractive for suppressing maladaptive V1 expression in activated cardiac fibroblasts. However, cardiac-specific *in vivo* versican knockdown has not been demonstrated using functional endpoints in myocardial disease models. Current ev-

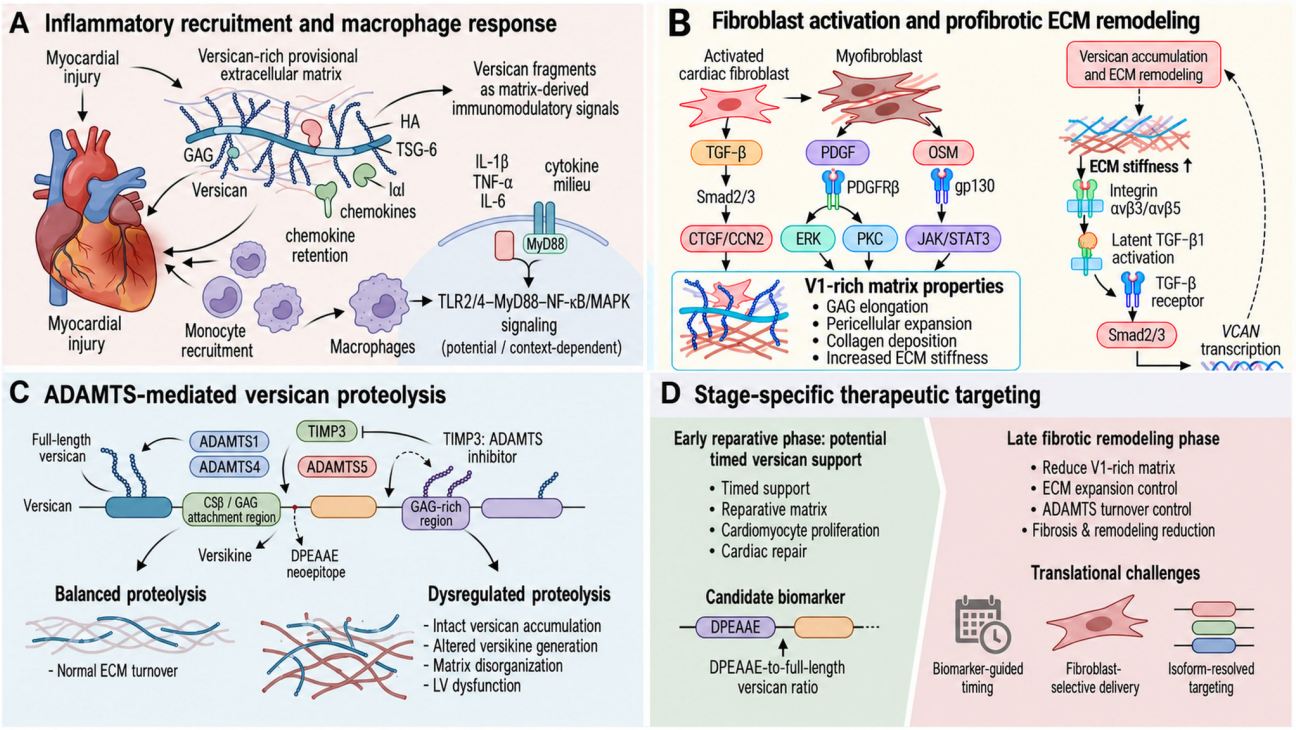


Fig. 2. Versican-mediated mechanisms and therapeutic implications in cardiac remodeling. (A) Versican-rich provisional ECM that formed after myocardial injury contributes to chemokine retention, monocyte/macrophage recruitment, and context-dependent inflammatory signaling. (B) Activated fibroblasts and myofibroblasts promote V1-rich versican matrix formation through profibrotic pathways, including TGF-β/Smad2/3, CTGF/CCN2-mediated regulation, PDGF–PDGFRβ signaling via ERK and PKC, OSM–gp130/JAK/STAT3, and integrin-mediated mechanotransduction. (C) ADAMTS-mediated versican proteolysis generates versikine and DPEAAE-containing neoepitopes; balanced proteolysis supports ECM turnover, whereas dysregulated proteolysis may contribute to matrix disorganization and left ventricular dysfunction. (D) Stage-specific therapeutic strategies may include early timed versican support and late-stage control of V1-rich matrix accumulation, ECM expansion, and abnormal proteolysis, with biomarker-guided timing, fibroblast-selective delivery, and isoform-resolved targeting as potential translational directions. ADAMTS, A disintegrin and metalloproteinase with thrombospondin motifs; CTGF/CCN2, connective tissue growth factor/cellular communication network factor 2; ECM, extracellular matrix; GAG, glycosaminoglycan; gp130, glycoprotein 130; HA, hyaluronan; IαI, inter-α-inhibitor; JAK, Janus kinase; OSM, oncostatin M; PDGF, platelet-derived growth factor; PDGFRβ, platelet-derived growth factor receptor–β; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-β; TLR, Toll-like receptor; TSG-6, tumor necrosis factor–stimulated gene-6; VCAN, versican. Note:This figure is an original schematic created by the authors using generative AI tools. No copyrighted images were reproduced.

idence is largely limited to conditional fibroblast-specific *VCAN* deletion, which establishes a requirement for versican in neonatal cardiac regeneration but does not directly address therapeutic suppression in adult fibrotic hearts [8]. Therefore, the feasibility of extrapolation from non-cardiac systems remains uncertain. The development of delivery platforms capable of achieving efficient, temporally controlled, and cardiac fibroblast–selective targeting is essential before versican-directed gene-silencing strategies can be translated.

4.3 Isoform-Selective Targeting: Structural Determinants and Therapeutic Constraints

Versican splice isoforms (V0–V3) generated through the differential inclusion of GAG-binding domains as outlined above exhibit distinct structural and functional properties with direct implications for therapeutic targeting. In particular, isoforms enriched in chondroitin sulfate (CS) chains contribute to the formation of an expanded pericellular matrix, whereas GAG-deficient variants such as V3 may act as competitive regulators of matrix assembly by occupying HA-binding sites without supporting matrix expansion [3,22]. These differences suggest potential opportunities for isoform-selective interventions, including the modulation of alternative splicing or targeting of isoform-associated GAG structures.

However, this concept is largely theoretical. To date, no isoform-specific antibodies, aptamers, or validated targeting strategies have been established for the cardiac system. Moreover, although CS chains vary in abundance, do-

main localization, and sulfation patterns across isoforms, their marked structural heterogeneity and dynamic remodeling limit their utility as reliable isoform-specific therapeutic epitopes [3,54]. Accordingly, the isoform-selective targeting of versican remains an unresolved challenge requiring the development of isoform-resolved molecular tools and rigorous validation in cardiac-specific models before clinical translation can be considered.

5. Conclusions

In summary, versican is increasingly being recognized as an active regulator of cardiac remodeling rather than a passive ECM component. Moreover, its expression in injured or pressure-overloaded hearts is dynamic and highly context-dependent. Early versican accumulation may support matrix organization, inflammatory cell recruitment, and reparative responses, whereas persistent V1-enriched deposition is associated with fibroblast activation, pericellular matrix expansion, profibrotic signaling, and adverse remodeling. ADAMTS-mediated proteolysis further modifies versican function by generating bioactive fragments such as versikines and DPEAAE-containing products, thereby contributing to proteoglycan-rich matrix turnover and cardiac structural integrity.

However, several issues remain unresolved. The disease-specific roles of the V0–V3 isoforms, mechanisms governing isoform switching and glycosaminoglycan modification, and spatial relationship between versican deposition and proteolysis are not completely understood. Whether versican directly modulates macrophage polarization and fibroblast activation or influences these processes by remodeling the ECM microenvironment requires further investigation. In particular, the functions of versican-derived fragments in infarcted and fibrotic myocardia require elucidation.

These uncertainties have important therapeutic implications for versican-directed interventions in cardiac remodeling. Because versican may exert reparative effects in the early phase of injury but contributes to fibrosis and adverse remodeling when persistently accumulated, future interventions should be stage-specific rather than broadly inhibitory. Strategies aimed at enhancing early reparative signaling or limiting late V1-dominant matrix expansion and dysregulated ADAMTS-dependent turnover may provide new opportunities for targeted therapies. Progress in this field will depend on validated biomarkers, cardiac fibroblast-selective delivery approaches, and isoform-resolved tools capable of distinguishing beneficial reparative versican functions from maladaptive fibrotic effects.

Author Contributions

YC, JL contributed to the conceptualization of the review. YC performed the initial literature search and wrote the original draft. JL led the major revision process, including restructuring the manuscript, performing updated literature searches, and writing new sections. YC also designed and created the summary figure (Visualization). JL provided overall supervision, project administration, and critical revisions to the manuscript. JL was responsible for funding acquisition. Both authors contributed to the review and editing of the manuscript. Both authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT-5.5 to check spelling and grammar and to assist in the refinement and preparation of graphical elements of the manuscript. After using this tool, the authors reviewed and edited the content and graphical materials as needed, the authors used ChatGPT to generate Figs. 1,2 and take full responsibility for the content of the publication.

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