Review

Sweet, yet underappreciated: Proteoglycans and extracellular matrix remodeling in heart disease

Geir Christensen [a,b], **Kate M. Herum** [a,b,c] **and Ida G. Lunde** [a,b]

***a* - Institute for Experimental Medical Research,** *Oslo University Hospital and University of Oslo, Oslo, Norway*
***b* - K.G. Jebsen Center for Cardiac Research,** *University of Oslo and Center for Heart Failure Research, Oslo University Hospital, Oslo, Norway*
***c* - Department of Bioengineering,** *University of California San Diego, La Jolla, CA, United States*

Correspondence to Geir Christensen: *Institute for Experimental Medical Research, Oslo University Hospital and University of Oslo, Oslo, Norway. geir.christensen@medisin.uio.no.*
https://doi.org/10.1016/j.matbio.2018.01.001

Abstract

Extracellular matrix remodeling is extensive in several heart diseases and hampers cardiac filling, often leading to heart failure. Proteoglycans have over the last two decades emerged as molecules with important roles in matrix remodeling and fibrosis in the heart. Here we discuss and review current literature on proteoglycans that have been studied in cardiac remodeling. The small leucine rich proteoglycans (SLRPs) are located within the extracellular matrix and are organizers of the matrix structure. Membrane-bound proteoglycans, such as syndecans and glypicans, act as receptors and direct cardiac fibroblast signaling. Recent studies indicate that proteoglycans are promising as diagnostic biomarkers for cardiac fibrosis, and that they may provide new therapeutic strategies for cardiac disease.

Extracellular matrix in heart disease: increasing awareness of its importance

In healthy adult humans, the heart pumps about 300 l of blood every hour throughout a lifetime. During exercise the heart may pump an astonishing 1500 l per hour. The contracting cells of the heart, the cardiomyocytes, perform the active systolic contraction of the heart muscle, the myocardium [1]. Interestingly, accumulating scientific evidence has led to an increasing awareness about the crucial role of the extracellular matrix in development and function of the heart. Studies have shown that a decellularized heart containing only extracellular matrix can guide cardiac cells to form a complete normal structured and functional heart [2], illustrating the importance of the cardiac extracellular matrix. Numerous studies have brought the extracellular matrix to the center stage of cardiac development and function, constituting the structural scaffold as well as holding biological signals directing the cells of the heart, mainly the cardiomyocytes and cardiac fibroblasts [3].

In cardiac disease, alterations in size and shape of the heart, collectively referred to as remodeling, may be dramatic [1]. Cardiomyocytes typically increase in size during this process, or die. Remodeling of the extracellular matrix is often extensive (Fig. 1). In heart failure, a common consequence of diseases or conditions such as myocardial infarction, valvular heart disease or high blood pressure, remodeling of the extracellular matrix may increase cardiac stiffness to a level where the cardiac filling during diastole is restricted. The filling may be restricted to such an extent that the patients suffer and die of heart failure, a syndrome defined by the failure of the heart to pump blood to sufficiently serve the body. This type of heart failure with diastolic dysfunction is often referred to as heart failure with preserved ejection fraction (fraction of blood ejected from left ventricle during a heart beat; HFpEF), as opposed to heart failure with systolic dysfunction where the ejection fraction is reduced (HFrEF) [1]. The prognosis for heart failure is grim and only half of the patients are alive five years after diagnosis, despite

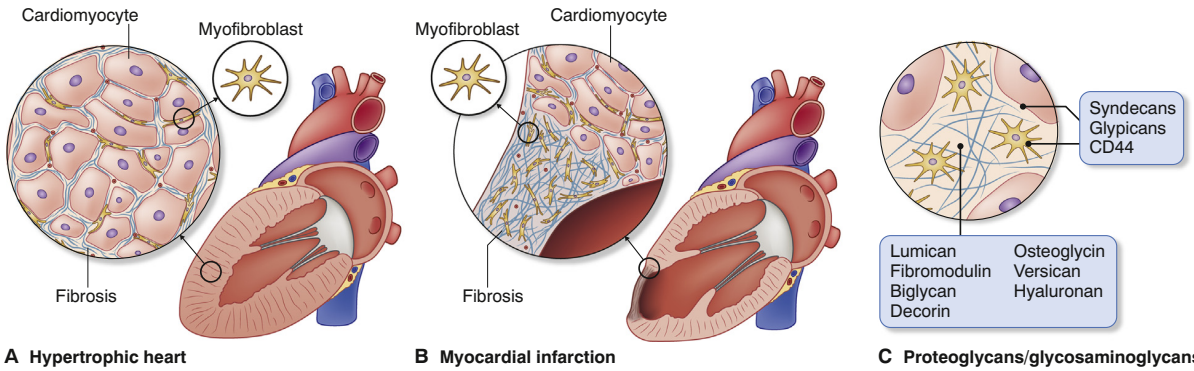

Fig. 1. Proteoglycans are important molecules in extracellular matrix remodeling in the heart. A Remodeling of the hypertrophic heart, with increased amount of extracellular matrix, fibrosis, and increased cardiomyocyte size. Fibroblasts are activated by pressure overload and transdifferentiate into myofibroblasts. B Fibrotic area of a heart following a myocardial infarction. C Proteoglycans/glycosaminoglycans located in the extracellular matrix or bound to membranes that have been studied in cardiac remodeling. Hyaluronan is not a proteoglycan *per se*.

state-of-the-art treatment. This has led to substantial efforts to elucidate the mechanisms regulating extracellular matrix remodeling, and to develop new methods for diagnosis and treatment of the fibrosis in the heart. Focus has been on identifying molecules that initiate and maintain remodeling of the cardiac extracellular matrix, and proteoglycans have emerged as particularly important molecules [3–7].

Here we discuss current literature on the proteoglycans that until now have been studied in cardiac extracellular remodeling (Fig. 1C), and the hitherto underappreciated roles of proteoglycans in the heart. In the final part of the review, diagnostic and therapeutic opportunities are discussed.

Proteoglycans in matrix remodeling and heart disease: new light on sugar-containing proteins

Over the last decades, proteoglycans have been shown to be involved in pathological remodeling of the extracellular matrix in common diseases of the heart [3–6]. Proteoglycans are glycosylated proteins [8]. They consist of a core protein with covalently attached glycosaminoglycan (GAG) chains. The GAG chains are linear carbohydrate polymers with a repeating disaccharide unit. They have a high degree of heterogeneity with regards to molecular mass, disaccharide construction and sulfation, regulated by several specific processing enzymes [9,10]. The GAG chains determine, to a large degree, the function of proteoglycans. GAGs are among the most negatively charged molecules in mammalian tissues, allowing for reversible and irreversible interactions with positively charged partners including matrix proteins, cytokines, chemokines, pathogens, growth factors and proteases. For instance, heparan sulfate, a GAG found on many proteoglycans in the heart, is essential for animal life [11]. All cells in the body are covered with a carbohydrate gel called the glycocalyx, where the main constituents are heparan sulfate bound to proteoglycans, the polysaccharide hyaluronan and proteins bound to these polysaccharides [12]. The anticoagulant heparin, one of the most effective, cheap and safe medicines in the health system, is, in fact, the naturally occurring heparan sulfate GAG produced by mast cells [13,14]. Crucial for its function, it carries the highest negative charge density of any known biological molecule.

Since proteoglycans have specific roles during cardiac remodeling, understanding their functional and mechanistic roles requires a reductionist scientific approach. We here discuss the main studies that have examined proteoglycans in cardiac remodeling. As heparan sulfate is a major constituent of the extracellular matrix with a key role in maintaining its function and integrity, the role of its degrading enzyme heparanase will be discussed in light of pathophysiological processes in the heart. Enzymes regulating proteoglycan cleavage, resulting in shedding of a part of the proteoglycan or its degradation, include a family termed ADAMTS, short for a disintegrin and metalloproteinase with thrombospondin motifs [15], that will be discussed in more detail due to their potential as therapeutic targets.

A comprehensive classification of proteoglycans has been provided by Iozzo & Schaefer [8], and is based on cellular and subcellular location, overall gene/protein homology and specific protein modules in the protein cores. The proteoglycans that have been studied in extracellular matrix remodeling in the heart belong to those located at the cell surface and those within the extracellular matrix (Fig. 2). The cell surface proteoglycans are the transmembrane, *i.e.* syndecans, CD44, and the GPI-anchored glypicans. The extracellular proteoglycans that have been studied in cardiac remodeling are the hyalectans,

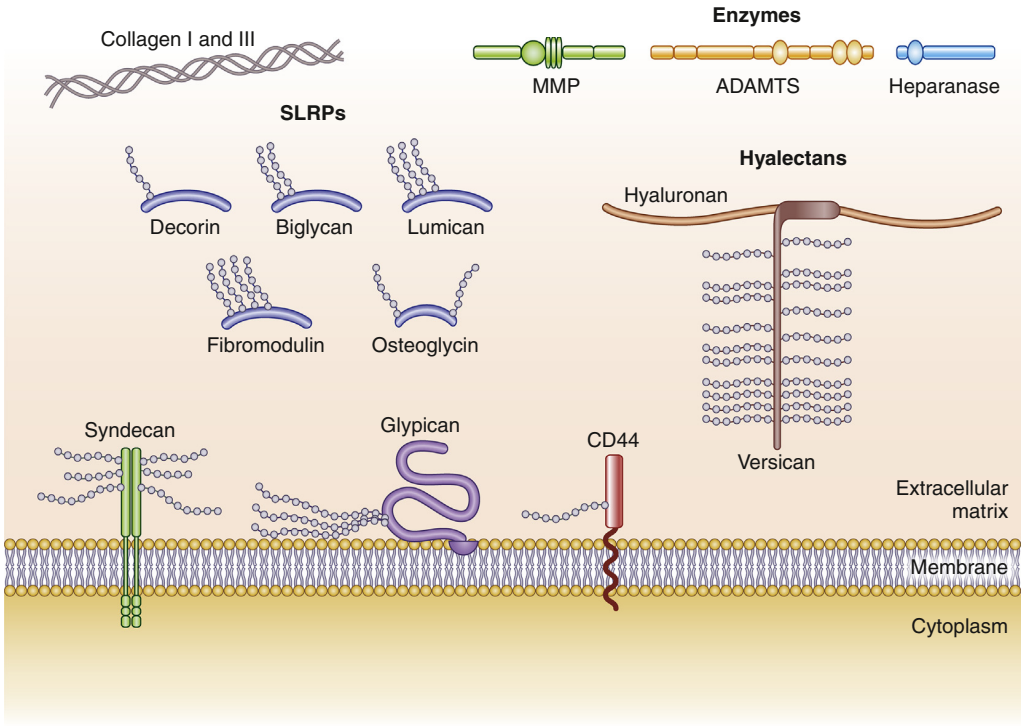

Fig. 2. Proteoglycans and related enzymes involved in cardiac remodeling. The family of small leucine-rich proteoglycans (SLRPs) and hyalectans are located within the extracellular matrix, whereas syndecans, glypicans and CD44 are membrane-bound. All SLRPs shown have leucine-rich-repeats. Decorin is predominantly a dermatan sulfate proteoglycan, biglycan a chondroitin sulfate proteoglycan, and lumican and fibromodulin keratan sulfate proteoglycans. Syndecans have PDZ-domains and are predominantly heparan sulfate proteoglycans. Glypicans are also predominantly heparan sulfate proteoglycans. CD44 is a heparan sulfate/chondroitin sulfate proteoglycan. Protein modules in versican are proteoglycan tandem repeat, EGF-like, IgG, C-type lectin and complement binding protein, and it is substituted with chondroitin sulfate glycosaminoglycan (GAG) chains. Proteoglycans are post-translationally modified and degraded by the enzymes matrix metalloproteinase (MMP) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) families. Heparanase specifically degrades heparan sulfate GAGs. Collagen I and III are the most abundant collagens in the extracellular matrix of the heart.

characterized by an N-terminal domain that binds hyaluronan and a C-terminal domain that binds lectins, *e.g.* versican, and the small leucine rich proteoglycans (SLRPs), characterized by modules containing leucine-rich repeats (LRRs), *e.g.* biglycan, decorin, fibromodulin, lumican and osteoglycin.

Syndecans and SLRPs are believed to play important roles in cardiac remodeling [3–6]. These proteoglycans regulate the hypertrophic growth of cardiomyocytes, inflammation, the activation and pro-fibrotic activity of cardiac fibroblasts, and organization of the extracellular matrix. Thus, they are central for matrix remodeling in the heart.

Extracellular proteoglycans: organizers of matrix structure and activators of fibroblasts

The SLRP family constitutes a group of low molecular weight, secreted proteoglycans named for their LRRs [8]. SLRPs were identified in bone and cartilage [16], and are now known to be expressed in numerous tissues, including the heart. SLRPs bind collagen fibrils, and influence collagen fibrillogenesis through regulation of collagen fibril diameter and interfibrillar spacing in the extracellular matrix [17]. SLRPs are also believed to be necessary for normal heart and heart valve formation during development [18]. A study from our group suggests that SLRPs are important in the adult heart, as reduced SLRP levels upon pressure overload were associated with loosely packed extracellular matrix and severe cardiac dilatation in mice [19]. Members of the SLRP family that have been studied in heart include lumican, fibromodulin, biglycan, decorin and osteoglycin.

Lumican is an organizer of the cardiac extracellular matrix

Lumican shows high expression in the heart and eyes of adult mice. Interestingly, a recent study has

reported that lumican knock-out mice show increased mortality with reduced systolic function during age-induced structural remodeling of the heart [20]. Thus, the hypothesis that lumican knock-out mice show an exacerbated heart failure phenotype upon pathological stimuli should be the focus future studies. Interestingly, lumican is abundant in fibrotic tissues including the thickened intima of human coronary arteries resulting from atherosclerosis and in ischemic hearts [21]. Our group has shown that lumican levels are increased in dilated hearts of patients with HFrEF and mice in response to pressure overload [22,23]. Its expression in cardiac fibroblasts is increased by mechanical stretch, interleukin (IL)-1β and lipopolysaccharide (LPS) [22], important stimuli for cardiac extracellular matrix remodeling and inflammation. Lumican binds collagens and is important for collagen organization [24]. This was clearly shown in studies of lumican knock-out mice revealing that lumican is crucial for organization of collagen fibrils in the cornea, and thus, its transparency [24]. A similar role in organization of collagen in the heart and during development of cardiac disease is anticipated, but has not been shown.

In addition, a direct effect of lumican on cardiac cells is likely. Treatment of cultured cardiac fibroblasts with recombinant lumican induced the expression of collagen I, suggesting a pro-fibrotic effect in the heart [22]. In line with this, lumican also affects cellular expression and post-translational modification of molecules central to cardiac remodeling, *i.e.* levels of the collagen cross-linking enzyme lysyl oxidase (LOX), transforming growth factor (TGF)β, smad phosphorylation and matrix metalloproteinase (MMP)9 activity. Thus, the hypothesis that lumican promotes myocardial fibrosis during heart failure progression should be tested in an *in vivo* experimental setting, assessing whether lumican directs myocardial stiffness, dilatation, cardiac function and pro-fibrotic molecular programs.

Fibromodulin levels are increased in the failing heart, but its potential role remains unknown

Fibromodulin, like lumican, is a collagen-binding SLRP widely expressed in connective tissues and believed to be involved in development of fibrosis [24]. Fibromodulin is found in heart valves and plays a role in their development alongside other SLRPs [18]. It is also expressed in the myocardium, and is upregulated in left ventricular pressure overload after aortic banding in mice [22], suggesting a role in cardiac remodeling and heart failure progression. Studies on the role of fibromodulin in the heart are scarce, and thus, fibromodulin is an interesting candidate for future studies investigating hypotheses related to its role in cardiac extracellular matrix remodeling.

Biglycan and decorin are regulators of collagen fibrillogenesis and fibrosis

Biglycan and decorin share the highest homology among SLRPs and carry GAG chains of chondroitin or dermatan sulfate [8,25]. Both are expressed in the healthy heart and their levels increase in experimental models of heart failure, *e.g.* after myocardial infarction and pressure overload [19,22,23,25–28]. In humans, biglycan and decorin levels are increased in explanted hearts from patients with terminal HFrEF [22], and biglycan has been detected in the healed infarct scar, co-localizing with tightly packed collagen fibers [29]. They bind collagens and regulate fibrillogenesis, suggesting that they regulate extracellular matrix integrity, tensile strength and fibrosis.

A central finding is that biglycan is up-regulated in the fibroblast cell population of the heart, and not cardiomyocytes, leukocytes or endothelial cells, after pressure overload [26]. Upon pressure overload, biglycan knock-out mice show attenuated hypertrophic growth and fibrosis, with improved cardiac function [26]. Upon myocardial infarction, biglycan knock-out mice show increased mortality due to cardiac rupture, increased dilatation, less tensile strength and severely impaired collagen matrix organization [29]. These studies clearly show that biglycan is important for extracellular remodeling in the heart, affecting cardiac function and animal survival. Biglycan has been reported to stimulate innate immunity pathways through toll-like receptors (TLRs), suggesting innate immunity responses as downstream pathways [17]. Indeed, an emerging body of evidence suggests that extracellular matrix proteoglycans and their enzymatically-modified fragments can activate TLRs, thereby modulating downstream innate immunity signaling pathways and remodeling processes [30].

Decorin is known to interact with growth factors and inhibits TGFβ bioactivity by sequestration, and by reducing TGFβ expression [31]. In human cardiac fibroblasts *in vitro*, decorin decreases collagen production after TGFβ stimulation [32]. Interestingly, decorin gene transfer neutralizes TGFβ in mouse cardiac tissue transplants, attenuating interstitial fibrosis and adverse remodeling [33]. Consistent with the anti-fibrotic effect of decorin, its overexpression leads to reduced myocardial fibrosis and improved cardiac function in hypertensive rats through inhibition of TGFβ and smad signaling pathways [34]. Decorin also regulates angiogenesis and may thereby possibly affect the recovery of cardiac function following injury [35].

Osteoglycin is a regulator of collagen cross-linking in the heart

Osteoglycin, also called mimecan, is critical for proper collagen assembly in the diseased heart [36]. Osteoglycin exists in multiple variants with altered glycosylation states and different functions [37], of

which the 20, 34, and 50 kDa forms are expressed by cardiac cells [36,38,39]. Osteoglycin knockout mice have markedly increased mortality post-infarction due to deficient scar formation and consequently, cardiac rupture [36]. Adenoviral overexpression of osteoglycin improved collagen assembly and protected against cardiac dilatation and dysfunction after myocardial infarction in mice. This effect was attributed to the physical bridging of collagen fibrils with osteoglycin, thereby creating non-enzymatic collagen cross-links that stabilize the infarct scar tissue [40]. Interestingly, the effect of osteoglycin on survival was only apparent in male mice, possibly pointing to sex-specific differences in extracellular matrix remodeling [36]. In agreement, higher levels of osteoglycin were detected in fibrotic scars of male patients compared to females recovering from myocardial infarction.

Recent data show the existence of a novel 72 kDa variant of osteoglycin resulting from chondroitin sulfate GAG chain substitution of the osteoglycin core protein. This isoform is expressed by circulating and resident immune cells in the heart following an inflammatory insult such as LPS-induced endotexemia and myocarditis [38]. Interestingly, this isoform binds to and activates TLR4, thereby potentiating immune cell responses. Thus, osteoglycin seems to be involved in inflammation in addition to its effects on collagen maturation and cross-linking.

Versican is produced by cardiac cells, but its role in cardiac remodeling remains to be explored

Hyalectans constitute a group of large extracellular proteoglycans which got their name from their ability to bind hyaluronan and lectins [8,41]. They reside in the extracellular matrix as high molecular weight aggregates with numerous and long GAG chains, interacting with structural and non-structural proteins and controlling tissue permeability, hygroscopicity and compressibility.

Versican has been extensively studied in connective tissues such as cartilage due to its hygroscopic properties, regulating water content of the tissue and providing shock-absorbing properties. Versican is expressed in the heart, although little is known about its function except for it being an essential part of normal cardiac development [42,43]. A study from our group shows that versican is up-regulated in the myocardium of rats with preserved or reduced contractile function after aortic banding [44]. The hygroscopic and viscoelastic properties of versican may influence myocardial function. Accumulation of the versican p150 fragment in the cardiac extracellular matrix may cause an unfavorable increase in myocardial water content. Indeed, heart failure has been associated with myocardial edema [45]. Thus, inhibiting ADAMTS4 versicanase activity may represent a novel therapeutic strategy [44] that will be discussed in the last part of this review.

Versican is produced by cardiac fibroblasts as well as myocytes, and its expression is enhanced by IL-1β and tumor necrosis factor (TNF)α, putting versican expression, as for several of the other proteoglycans expressed in the heart, under inflammatory control. A role in inflammation is supported by the finding that versican, by binding to hyaluronan, promotes leukocyte adhesion and their production of cytokines, and by versican being produced also by immune cells [46].

Hyaluronan is essential for mechanical integrity of the heart

Even though hyaluronan, also called hyaluronic acid, is not a proteoglycan *per se* as it does not have a core protein, but is itself a long GAG chain, and as such, is included in this review. Hyaluronan is of major importance for matrix remodeling and mechanical integrity of the matrix and is produced by the plasma membrane enzymes hyaluronic acid synthase (HAS) 1, 2 and 3 and degraded mainly by hyaluronidase 1 and 2. It retains large amounts of water due to its negative charge and large size, thus supplying mechanical support to the myocardium which is of major importance for cardiac development and remodeling. This is reflected in that genetic deletion of HAS2 is embryonic lethal due to severe cardiac malformations [47]. Deficiency in hyaluronidase 2 was recently linked to heart failure [48], suggesting that a balanced turnover of hyaluronan is necessary for cardiac physiology. Furthermore, low molecular weight fragments of hyaluronan have been associated with inflammation and activation of TLRs in other tissues [49], while high molecular weight hyaluronan has an anti-proliferative effect on immune cells [50]. Thus, degradation of hyaluronan into smaller fragments may constitute a danger alert mechanism that signals to cardiac cells to initiate remodeling of the extracellular matrix.

Membrane-bound proteoglycans: cell surface receptors and mediators of signaling

Recent data has revealed an important role for syndecans in matrix remodeling of the heart [5]. There are four members of the syndecan family (syndecan-1, -2, -3 and -4), all of which are expressed in the myocardium where they become upregulated following myocardial infarction [51] and left ventricular pressure overload [52]. Syndecans consist of a short cytoplasmic tail, a transmembrane domain and an extracellular domain with chondroitin or heparan sulfate GAG chains [8,53,54]. Interestingly, syndecan-1 and -4 have also been detected in the nucleus of non-cardiac cell types, including skeletal muscle, where they are suggested to regulate

proliferation and differentiation [55,56]. Thus, syndecans seem to regulate cell and organ function at multiple cellular and extracellular locations.

In the heart, syndecan-1 and syndecan-4 responses have been studied to date [52,57–63]. Syndecan-1 and -4 knockout mice display reduced production, impaired organization and compromised collagen cross-linking after myocardial infarction, pressure overload and angiotensin II infusion, leading to increased susceptibility to cardiac rupture [57,64], reduced myocardial stiffness [63] and exacerbated heart failure [57,62]. Common to syndecan-1 and -4 is their importance in maintaining extracellular matrix integrity during cardiac remodeling. However, there appears to be differences in the underlying mechanisms.

Syndecan-1 regulates cardiac fibroblast physiology through TGFβ signaling

Activation of the renin-angiotensin system is one of the hallmarks of heart disease, has pro-fibrotic effects in the heart and activates TGFβ [65]. Importantly, syndecan-1 is essential for angiotensin-induced cardiac fibrosis. Syndecan-1 is up-regulated in fibrotic areas of the heart after angiotensin II infusion [58], while syndecan-1 knockout mice show attenuated collagen expression and cardiac fibrosis through inhibited TGFβ-Smad2 signaling. Moreover, syndecan-1 knockout mice exhibit a higher risk of myocardial rupture upon myocardial infarction, due to abnormal collagen structure and inflammatory response, properties that were improved by syndecan-1 overexpression [57]. Adenoviral overexpression of syndecan-1 in rats supports the connection between syndecan-1 and TGFβ [59] through regulation of p38, a downstream mediator of TGFβ signaling that recently was demonstrated to be crucial for cardiac fibroblast pro-fibrotic activity [66]. Collectively, these results suggest that syndecan-1 is important for extracellular matrix remodeling through regulation of pro-fibrotic signaling pathways such as TGFβ-Smad2 and p38.

Syndecan-4 promotes cardiac myofibroblast differentiation and collagen cross-linking

Syndecan-4 is essential for cardiac myofibroblast differentiation after pressure overload [60] and myocardial infarction [64]. Myofibroblasts derive mainly from resident cardiac fibroblasts [67] and are specialized contractile fibroblasts with substantial pro-fibrotic activity that are promoted by TGFβ signaling and mechanotransduction signaling. Syndecan-4 is located at focal adhesions, areas that are believed to conduct mechanotransduction signaling, where it physically links the cytoskeleton to the extracellular matrix [4]. Cardiac fibroblasts from syndecan-4 knockout mice have reduced activity of signaling molecules associated with cytoskeletal dynamics, including focal adhesion kinase (FAK), protein kinase B (Akt) and the small GTPase RhoA [64]. Furthermore, we have shown that syndecan-4 is dephosphorylated on its cytoplasmic domain in response to mechanical stress [60,62], resulting in activation of calcineurin-NFAT (nuclear factor of activated T-cells) signaling and thus, myofibroblast differentiation and collagen expression. In this way, syndecan-4 may function as a molecular switch that activates pro-fibrotic signaling in response to mechanical stress [60].

Interestingly, syndecan-4 was recently shown to negatively regulate the activity of the Ca^{2+}-permeable channel transient receptor potential canonical (TRPC) 7 at focal adhesions, promoting myofibroblast differentiation [68]. Along these lines, Ca^{2+} influx through TRPC6 channels has been shown to activate calcineurin-NFAT signaling and be necessary for TGFβ-induced myofibroblast differentiation [69]. Collectively, these data suggest a connection between syndecan-4 and Ca^{2+} signaling although it is yet to be determined whether this is important for cardiac myofibroblast differentiation and matrix remodeling of the heart.

The attenuated myocardial stiffness in syndecan-4 knockout mice following pressure overload was attributed to reduced expression of the collagen cross-linking enzyme LOX [63]. Furthermore, electron microscopy of collagen fibers *in vitro* indicated a direct role for the extracellular domain of syndecan-4 in regulating collagen fiber assembly and facilitating collagen cross-linking by LOX [63]. Indeed, collagen assembly and cross-linking are impaired in syndecan-4 and -1 knockout mice following pressure overload and myocardial infarction, respectively [57,63], although in syndecan-1 knockout mice this was attributed to reduced activity of the collagen cross-linking enzyme tissue transglutaminase [57] as a consequence of increased myocardial inflammation in these mice.

Syndecans fine-tune inflammatory responses in the heart

Syndecans are central for the onset, progression and resolution of inflammation [70,71]. Sterile inflammation is part of heart failure progression [72,73] and is enhanced in mice lacking syndecan-1 following myocardial infarction. This is likely due to increased transendothelial adhesion and migration of leukocytes when syndecan-1 is lacking. Activation of the innate immune system also leads to upregulation of syndecan-4 through IL1β, TNFα and NF-κB, and increases shedding of the syndecan-4 ectodomain [61]. Moreover, syndecan-4 seems to be important for immune cell recruitment as infiltration of T-cells was impaired in syndecan-4 knockout mice following pressure overload [61]. Importantly, T-cells are associated with collagen cross-linking in the heart [74]

and thus, it is likely that syndecan-4 also regulates collagen cross-linking by promoting immune cell infiltration. In agreement, our recent results demonstrate upregulation of immune cell adhesion molecules, *i.e.* intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule (VCAM-1), in cardiac myocytes and fibroblasts treated with shed ectodomains of syndecan-4 [61]. Taken together, syndecans seem to be important regulators of cardiac inflammation, albeit the effects and mechanisms are distinct for syndecan-1 and -4.

Glypicans are important in congenital heart disease

Glypicans (GPC1-6) constitute the other main family of membrane-bound proteoglycans, they carry heparan sulfate GAGs, are evolutionary ancient and highly conserved among species [8,75–77]. Glypicans lack a cytoplasmic domain, and are covalently anchored to the extracellular part of the cell membrane through a glycosylphosphatidylinositol (GPI) anchor. The heparan sulfate chains on glypicans are attached to the core protein close to the cell membrane and, similar to syndecans, the extracellular part of glypicans can be enzymatically shed from the cell surface. All glypicans except GPC5 are expressed in the heart [78–80]. Mutations in the GPC3 and GPC6 genes cause rare growth disorders, *i.e.* the Simpson-Golabi-Behmel overgrowth syndrome and the generalized omodysplasia (OMOD1) dwarfism syndrome, respectively [81–85]. Congenital heart defects have been reported in both syndromes [86,87], indicating important roles of GPC3 and GPC6 in the heart. Supportive of a role for GPC3 in heart disease, GPC3 knock-out mice show high incidence of congenital heart malformations such as ventricular-septal defects (VSD), common atrioventricular canal, double outlet right ventricle and coronary artery fistulas [88]. Glypicans are believed to be important during development through regulation of Wnt, Frizzled and Hedgehog signaling [75,77,89], and the GPC-dependent congenital heart defects are likely associated with dysregulation of these pathways.

Little is known about the role of glypicans in heart failure progression and cardiac extracellular matrix remodeling. Our group recently showed that GPC1-3 and -6 show altered expression during cardiac remodeling in mice in response to pressure overload [80]. We focused on GPC6 due to its sustained up-regulation during hypertrophic remodeling and end-stage, dilated heart failure. In line with the impaired growth of OMOD1 patients lacking functional GPC6, we found that overexpression of GPC6 in cardiomyocytes resulted in hypertrophic growth and activation of ERK1/2 signaling. GPC6 is produced by both cardiac fibroblasts and myocytes. Its higher expression in cardiac fibroblasts, and its up-regulation by angiotensin II and bone morphogenetic protein (BMP) 4 (a member of the TGF superfamily), is supportive of a role in cardiac extracellular matrix remodeling. Glypicans regulate cellular responses to growth factors regulating cell migration, differentiation and proliferation, and of particular relevance to cardiac extracellular matrix remodeling, is their regulation of fibroblast growth factor (FGF) signaling [75,76]. *In vitro,* our studies show that GPC6 affects cardiac fibroblast ERK1/2 signaling, however we did not observe effects on fibroblast collagen expression, proliferation or migration [80]. The hypothesis that glypicans play a role in fibrosis and extracellular matrix remodeling in the heart *in vivo* remains to be studied.

The role of heparanase in cardiac disease remains unknown

Heparanase (HPSE) is the only known mammalian endoglycosidase capable of degrading heparan sulfate [12,90,91]. Heparan sulfate is a major constituent of membrane-bound proteoglycans, glycocalyx and extracellular matrix with a key role in maintaining their functional integrity and bioavailability of growth factors including TGFβ. Heparan sulfate is found mainly in the form of syndecans, glypicans and hyaluronan. Heparanase has endoglycosidase activity and cleaves heparan sulfate into oligosaccharide fragments of 10–20 sugar units. In most tissues and cells, except the placenta, platelets, keratinocytes and activated immune cells, the heparanase promoter is constitutively silenced [91]. However, upon pro-inflammatory mediators such as IL1β, TNFα and NF-κB, heparanase expression is dramatically induced [92–94]. Whether this is the case in cardiac fibroblasts and myocytes, remains to be explored. Endothelial and immune cells are known sources of heparanase in the heart [95,96], and heparanase levels are increased during hypertrophic remodeling [97,98]. When induced, heparanase facilitates heparan sulfate turnover and recycling, thereby remodeling the glycocalyx and matrix during for instance inflammatory processes. Given the potential for heparanase to disrupt the matrix and cell surface signaling processes, its activity is tightly regulated. Although its role on cardiac fibrosis has not been investigated, recent studies demonstrate that heparanase promotes fibrosis in several organs [99,100]. In the kidney, increased heparanase activity regulates epithelial-to-mesenchymal transition, fibroblast-myofibroblast transition and fibrosis [12,101–103]. That heparanase plays a role in cardiac fibrosis and matrix remodeling is an attractive area for research.

CD44 is associated with pro-fibrotic activity of cardiac fibroblasts

CD44 is a transmembrane part-time proteoglycan originally known for its role in lymphocytes, but has since shown to be expressed by a wide range of cells including those of the heart [104]. It is the main

receptor for hyaluronan and is upregulated in the inflammatory phase after an acute myocardial infarction [104] and downregulated in HFrEF patients [105]. CD44 knockout mice exhibit prolonged inflammation, reduced fibroblast infiltration, collagen synthesis and myofibroblast differentiation, and enhanced ventricular dilatation following myocardial infarction [104], supporting a role for CD44 in regulating proliferation and migration of cells in tissues where hyaluronan is abundant [106]. CD44 is thought to exert intracellular signaling through interaction with growth factor receptors including the receptor for TGFβ [107]. This is supported by a recent report showing a hyaluronan-dependent direct interaction between CD44 and TGFβ receptors, and a crucial role for CD44 in TGFβ-induced collagen synthesis and myofibroblast differentiation of lung fibroblasts [108]. Considering that the cardiac phenotype of CD44 knockout mice exhibit lack of these same features, it seems likely that CD44 regulates TGFβ-induced fibrosis also in the heart.

Circulating proteoglycans as diagnostic indicators of cardiac fibrosis

The presence of extracellular matrix remodeling and fibrosis in most cardiac diseases calls for clinically applicable methods to monitor this process in order to risk-stratify patients and optimize treatment. Currently, such methods are not routinely applied in the clinical evaluation of patients with heart failure or other cardiac diseases. Cardiac biopsies are used for assessment of collagen, and could be employed for measurements of other markers of fibrosis such as proteoglycans. However, biopsies are not readily available in most patients and thus, will not allow for longitudinal assessment of matrix remodeling. Techniques for assessment of fibrosis using magnetic resonance imaging (MRI) are currently being tested and validated in patients, with promising results [109,110]. MRI may become important for clinical assessment of cardiac fibrosis. However, circulating biomarkers are very reliable indicators in some cardiac diseases, for instance in acute myocardial infarction. Biomarkers that can be measured in blood, representing extracellular remodeling and fibrosis in the heart, would be a major step forward in the clinic with regards to diagnosis, prognosis and risk stratification in patients with heart disease.

Recent studies indicate that measurements of certain proteoglycans in tissue samples [111–113] and in blood [61,114–118] may provide valuable information in patients. Shed fragments of cardiac proteoglycans are promising candidate blood biomarkers in heart disease. Similarly, the N- and C-terminal collagen I and III fragments are being tested and validated as blood biomarkers of fibrosis. The enzymatically shed extracellular fragments of syndecan-1 and -4 have shown potential as biomarkers of cardiac disease. In one study [114], circulating levels of syndecan-1 correlated to cardiac function in patients with heart failure. The authors found a positive correlation between circulating syndecan-1, fibrosis and remodeling.

We have shown that syndecan-4 is produced in, and shed from, the failing human heart [52,61]. Recent data from our group demonstrate a higher plasma concentration of shed syndecan-4 locally in the heart of aortic stenosis patients [61], consistent with increased expression and shedding of syndecan-4 in left ventricular biopsies of patients with aortic stenosis [62] and heart failure patients [52]. In patients with acute myocardial infarction [115], chronic heart failure [116,117] and hypertension [118], blood syndecan-4 levels were increased. Syndecan-4 levels correlated positively with left ventricular mass indicating that syndecan-4 may reflect cardiac extracellular matrix remodeling.

Several other proteoglycans may also become useful as biomarkers. Osteoglycin, or mimecan, blood levels correlate with left ventricular mass [39]. Other studies have also provided promising data on prediction of ventricular remodeling using osteoglycin as a biomarker [119]. Moreover, Van Aelst et al. [36] showed that circulating osteoglycin levels in patients with heart failure were significantly higher in patients with history of myocardial infarction, and correlated with survival and markers of fibrosis. Thus, osteoglycin could be a promising blood biomarker in ischemic heart failure. Biglycan may also have a role as biomarker in cardiac disease. One study has shown that measuring serum levels of biglycan may be useful in identifying a subset of patient with heart failure who may benefit from lipid-lowering therapy with statins [120]. Taken together, proteoglycans provide new opportunities for assessing cardiac extracellular matrix remodeling using tissue or blood samples from patients.

Potential for proteoglycans as therapy in cardiac diseases

Treatment options specifically targeting cardiac extracellular matrix remodeling and fibrosis are scarce and insufficient. As mentioned in the introduction, the prognosis for heart failure patients is grim and only half of the patients are alive five years after receiving the diagnosis, despite state-of-the-art treatment. To reduce suffering and increase survival, new therapeutic targets are needed, particularly in HFpEF.

Injecting proteoglycan-containing extracellular matrix hydrogels made from decellularized pig hearts into myocardial infarcts through a transendocardial catheter is currently being tested clinically as a minimal invasive way to supply structural support the infarct and decrease subsequent adverse

remodeling (NCT02305602). Results from preclinical studies show that injection of hyaluronan or extracellular matrix-derived hydrogels improved cardiac function and remodeling in small and large animal models of myocardial infarction [121,122]. More specifically, hydrogel injection reduced cardiomyocyte apoptosis, increased neovascularization of the infarct and reduced interstitial fibrosis. This novel strategy may overcome adverse matrix remodeling and improve post-myocardial infarction cardiac physiology [123,124].

Inhibition of enzymes regulating proteoglycan turnover has in a recent study from our laboratory been shown to be effective in experimental heart failure [44]. During remodeling, proteoglycan turnover accelerates due to an enhanced activity of cleavage enzymes belonging to the matrix metalloproteases (MMP) and ADAMTS families. Previous attempts to target extracellular matrix turnover by MMP inhibitors have not been successful, partly due to harmful side effects in non-cardiac tissues. Heparanase deficiency in animals as well as pharmacological inhibition of heparanase protect against renal inflammation and fibrosis, making heparanase a promising treatment target in kidney disease [12,100–103]. Inhibition of heparanase activity using modified heparins, small molecule inhibitors and function-blocking monoclonal antibodies is considered attractive in novel anticancer therapies, and several compounds are currently being tested for therapeutic purposes [91,125]. Emerging evidence shows that heparanase activity contributes to progression of several diseases including inflammatory diseases, autoimmune diseases, diabetes and vessel pathologies, suggesting that therapeutic inhibition of heparanase holds promise in various clinical fields [91]. Heparanase as a target in cardiac disease has not been evaluated.

A subset of ADAMTS enzymes that cleave proteoglycans (proteoglycanases) seem to possess specific enzymatic activities [15,126], suggesting that this subfamily of enzymes is suited as therapeutic targets. We have demonstrated that the synthesis of proteoglycanases ADAMTS1, -4 and -8, and versican cleavage by ADAMTS increase in rats with remodeled and failing hearts, and that ADAMTS4 is upregulated in cardiac cells stimulated with cytokines associated with heart failure [44]. Although all ADAMTS enzymes upregulated in heart disease are potential targets for therapy, only inhibition of ADAMTS enzymes with pentosan polysulfate (PPS) has been investigated so far for treatment of heart disease. PPS, known to inhibit ADAMTS4 and ADAMTS5, reduced the cleavage of versican, which might be beneficial since versican serves as determinant of the extracellular volume [7,127–129]. Other known substrates of ADAMTS4 include syndecan-4, decorin, fibromodulin, and biglycan. PPS is a drug currently approved in humans for interstitial cystitis. It restored cardiac contractility and diminished heart failure in rats. Thus, regulation of proteoglycan turnover has potential in treatment of cardiac diseases with matrix remodeling.

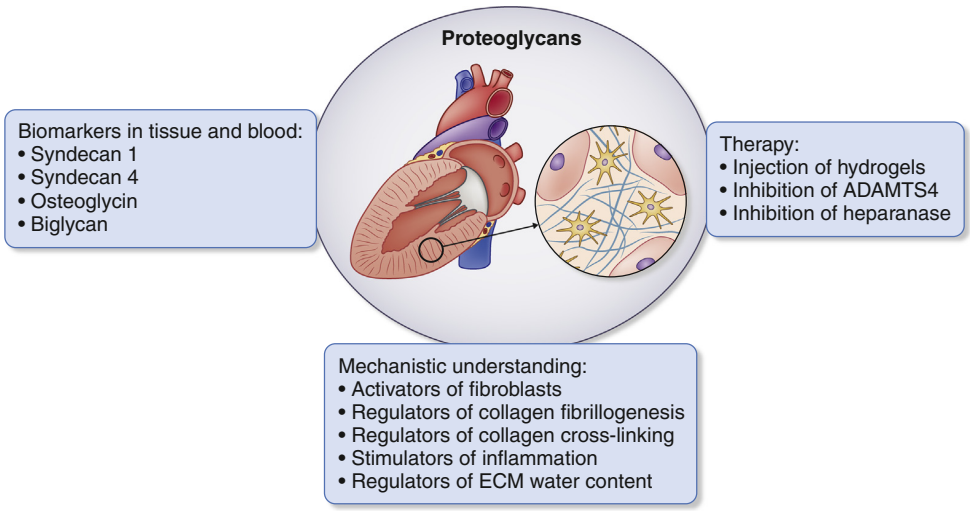

Fig. 3. Clinical implications of cardiac proteoglycan research. Studies indicate proteoglycans as biomarkers to be measured in tissue and blood that may reflect matrix remodeling and fibrosis. Moreover, studies indicate proteoglycans as new therapeutic targets for cardiac disease, such as inhibition of extracellular matrix (ECM) turnover. Increased mechanistic and functional understanding of the role of proteoglycans in cardiac disease is crucial for further progress towards the clinical use of proteoglycans, their fragments and related enzymes.

Final considerations

Proteoglycans play important roles in extracellular matrix remodeling and fibrosis in heart disease, and they are likely to emerge as diagnostic tools for cardiac fibrosis and to provide new opportunities for anti-fibrotic therapy to improve function of the heart (Fig. 3). It is, however, clear that more comprehensive mechanistic and functional understanding of proteoglycans in the heart is crucial for progress towards clinical use. With a continuation of the great progress that has been made over the last two decades on our understanding of proteoglycans in the heart, it is likely that proteoglycans will be appreciated in clinical cardiology in the years to come.

Acknowledgements

We thank the past and present members of the Christensen laboratory for their contributions to this body of knowledge. Our research is supported by The Research Council of Norway, Stiftelsen Kristian Gerhard Jebsen, Anders Jahre's Foundation for the Promotion of Science, South-Eastern Norway Regional Health Authority and Norwegian Health Association (K.M.H., I.G.L. and G.C.), Simon Fougner Hartmanns Family Fund, Denmark, Olav Raagholt and Gerd Meidel Raagholt's Fund for Science, Norway (I.G.L. and G.C.), and the European Commission Marie Curie Actions' COFUND program (K.M.H.). Artwork by Debbie Maizels, Zoobotanica Scientific Illustration.

Received 8 September 2017;
Received in revised form 22 November 2017;
Accepted 1 January 2018
Available online 12 January 2018

Keywords:
Proteoglycans;
Heart;
Heart failure;
Extracellular matrix;
Syndecan;
SLRP

Abbreviations used:
ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; Akt, protein kinase B; BMP, bone morphogenetic protein; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; FGF, fibroblast growth factor; GAG, glycosaminoglycan; GPC, glypican; GPI, glycosylphosphatidylinositol; GTP, guanosine triphosphate; HAS, hyaluronic acid synthase; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICAM, intercellular adhesion molecule; IL, interleukin; OMOD, omodysplasia; LOX, lysyl oxidase; LPS, lipopolysaccharide; LRR, leucine rich repeat; MMP, metalloproteinase; MRI, magnetic resonance imaging; NFAT, nuclear factor of activated T-cells; PPS, pentosan polysulfate; RhoA, Ras homolog gene family member A; SLRP, small leucine rich proteoglycan; Smad, small mothers against decapentaplegic; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; TRPC, transient receptor potential canonical; VCAM, vascular cell adhesion molecule; VSD, ventricular septal defects; Wnt, Wingless-type MMTV integration site family member.

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