International Journal of Cardiology 278 (2019) 192–198

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Emerging roles of proteoglycans in cardiac remodeling

Xiaoya Wang, Yi Lu, Yao Xie, Jian Shen, Meixiang Xiang *

Department of Cardiology, Second Affiliated Hospital, Zhejiang University School of Medicine, Key Lab of Cardiovascular Disease of Zhejiang Province, Hangzhou, Zhejiang 310009, PR China

ARTICLE INFO

Article history:
Received 6 October 2018
Received in revised form 12 November 2018
Accepted 27 November 2018
Available online 28 November 2018

Keywords:
Proteoglycan
Cardiac remodeling
Myocardial ischemia
Pressure overload
Heart failure

ABSTRACT

Cardiac remodeling is the response of the heart to a range of pathological stimuli. Cardiac remodeling is initially adaptive; however, if sustained, it ultimately causes adverse clinical outcomes. Cardiomyocyte loss or hypertrophy, inflammation and fibrosis are hallmarks of cardiac remodeling. Proteoglycans, which are composed of glycosaminoglycans and a core protein, are a non-structural component of the extracellular matrix. The lack of proteoglycans results in cardiovascular defects during development. Moreover, emerging evidence has indicated that proteoglycans act as significant modifiers in ischemia and pressure overload-related cardiac remodeling. Proteoglycans may also provide novel therapeutic strategies for further improvement in the prognosis of cardiovascular diseases.

1. Introduction

Cardiovascular disease affects millions of individuals worldwide and is the leading cause of death. Although the mortality of heart disease is significantly declining due to advances in interventional and pharmacological therapies, heart failure that results from adverse cardiac remodeling continues to lead to a poor clinical prognosis [1]. The most common preceding conditions that contribute to heart failure include myocardial ischemia in heart failure with reduced ejection fraction (HFrEF) and pressure overload in heart failure with preserved ejection fraction (HFpEF) [2,3]. Cardiac remodeling is a process that is initially compensatory; however, it eventually becomes detrimental when sustained. The pathological changes of cardiac remodeling include cell death, cardiomyocyte hypertrophy, inflammation, and excess extracellular matrix (ECM) accumulation [4]. Despite the tremendous efforts exerted in the research of cardiac remodeling, a great deal of questions remain to be clarified, particularly the role of proteoglycans.

Protein glycosylation is a process of posttranslational modification by adding sugars to proteins in the endoplasmic reticulum and Golgi apparatus [5]. Glycosylation contributes to stability, localization and function of proteins, and regulates many cellular processes, such as cell survival, differentiation and angiogenesis [6]. Proteoglycans are heavily glycosylated proteins and a major component of non-structural ECM. They distinguish themselves from other sugar-containing proteins by the glycosaminoglycans (GAGs) covalently attached to the protein core. GAGs are biologically active sugars, which may interact with various receptors and ligands thus both influence and enrich protein functionality [3]. There are five major groups of GAGs including chondroitin sulfate (CS), dermatan sulfate (DS), keratan sulfate (KS), heparan sulfate (HS)/heparin and hyaluronic acid (HA) [7]. Proteoglycans are classified into 4 groups according to the location: intracellular, cell surface, pericellular and extracellular proteoglycans [7]. Some proteoglycans are essential in the normal heart development and a deficiency in proteoglycans results in cardiovascular malformations [8]. Moreover, with the exception of intracellular proteoglycan, the remaining three types of proteoglycans are all involved in the pathogenesis of cardiac remodeling (Table 1 and Fig. 1).

We conducted a systematic search of the PubMed and EMBASE databases to identify studies to August 8th 2018. The terms used in the search are provided in the supplemental data. The titles and abstracts in English or Chinese were independently reviewed by two authors to select the relevant studies for further analysis. In the present narrative review, we will provide updated and comprehensive information regarding proteoglycans in major cardiac diseases that predispose to heart failure, as well as clarify the therapeutic application of proteoglycans in the clinic.

2. Proteoglycans in myocardial ischemia related cardiac remodeling

2.1. Proteoglycans attenuating pathological cardiac remodeling of myocardial ischemia

2.1.1. Syndecans: syndecan-1 and syndecan-4

Syndecans are a family of 4 transmembrane heparansulfate proteoglycans, which are composed of a conserved extracellular ectodomain, a transmembrane domain and a cytoplasmic domain [9]. Syndecans, particularly syndecan-1 (Sdc1) and syndecan-4 (Sdc4), have been shown to prevent adverse cardiac remodeling after myocardial ischemia [10].

* Corresponding author.
E-mail address: xiangmx@zju.edu.cn (M. Xiang).

https://doi.org/10.1016/j.ijcard.2018.11.125
0167-5273/

Table 1
Major findings on proteoglycans in cardiac remodeling studies.

Location	Classification	Eponym	Function	Disease models	Mechanisms	References
Cell surface	Transmembrane	Syndecan-1	Inflammation	-Myocardial infarction	-Monocyte chemoattractant protein-1	Lei et al. [13]
				-Aortic banding	-Leukocyte-endothelia interaction	Vanhoutte et al. [11]
					-p38 MAPK	Lunde et al. [52]
			Cardiomyocyte apoptosis	Myocardial infarction	-p38 MAPK	Lei et al. [13]
			Fibrosis	-AngII-induced cardiac hypertrophy	-TGF-β/Smad2	Schellings et al. [19]
				-Myocardial infarction	-MMPs	Vanhoutte et al. [11]
		Syndecan-4	Inflammation	-Myocardial infarction	-Immune cell recruitment	Xie et al. [12]
				-Aortic banding		Matsui et al. [18]
						Strand et al. [48,53,54]
						Lunde et al. [52]
			Fibrosis	-Myocardial infarction	-Myofibroblast differentiation	Matsui et al. [18]
				-Aortic banding	-Calcineurin/NFAT	Herum et al. [56,57]
			Cardiomyocyte hypertrophy	Aortic banding	Calcineurin-NFAT	Finsen et al. [45,50]
			Cardiomyocyte death	-Ischemia-reperfusion injury	-ERK	Echtermeyer et al. [14]
				-Myocardial infarction	-NFAT	Uryash et al. [15]
			Angiogenesis	Aortic banding	-↑PKCα activation	Li et al. [51]
		NG2	Cardiac fibrosis	Myocardial infarction	–	Offerhaus et al. [36]
		Betaglycan	Cardiomyocyte hypertrophy	-Aortic banding	-Calcineurin-NFAT	Lou et al. [69]
				-Isoproterenol-induced cardiac hypertrophy	-CaMKII	
			Cardiac fibrosis	Myocardial infarction	ERK1/2 & JNK pathway	Sun et al. [43]
			Cardiomyocyte apoptosis	Myocardial infarction	p38	Sun et al. [42]
	Glycosyl-phosphatidyl-inositol (GPI)-anchored	Glypican-6	Cardiomyocyte hypertrophy	Aortic banding	ERK1/2	Melleby et al. [70]
	Others	CD44	Inflammation	Myocardial infarction	-Immune cell recruitment	Huebener et al. [37]
					-Cytokine production	Iyer et al. [38]
					-Neutrophil apoptosis	
			Cardiac fibrosis	-Myocardial infarction	-Cardiac fibroblast proliferation	Huebener et al. [37]
				-Angiotensin II-induced cardiomyopathy	-TGF-β signaling	Yang et al. [39]
Pericellular	Basement membrane zone	Agrin	Cardiomyocyte proliferation	Myocardial infarction	Yap & ERK signaling	Bassat et al. [35]
		Perlecan	Angiogenesis	Myocardial infarction	FAX and p38 MAPK	Fu et al. [34]
		Collagen XVIII	Cardiac fibrosis	Myocardial infarction	MMP-2 and MMP-9	Isobe et al. [41]
		Collagen XV	Cardiac fibrosis	Isoproterenol-induced cardiac hypertrophy	Fibrillar collagen organization	Rasi et al. [68]
Extracellular	Hyalectan lectican	Versican	Inflammation	Myocardial infarction	-Immune cell adhesion	Mjaatvedt et al. [44]
					-Chemotaxis	
			Fibrosis	Myocardial infarction	-Fibroblast infiltration	Mjaatvedt et al. [44]
					-Collagen deposition	
	Small leucine rich proteoglycans	Biglycan	Cardiac fibrosis	-Myocardial infarction	-Collagen assembly	Westermann et al. [22,74]
				-Aortic banding	-Fibroblast transdifferentiation	Beetz et al. [71]
			Cardiomyocyte hypertrophy	Aortic banding	Hypertrophic gene activation	Beetz et al. [71]
			Cardiomyocyte death	–	-TLR4	Gorbe et al. [30]
					-Nitric oxide synthase	Gaspar et al. [31]
		Decorin	Cardiac fibrosis	-Spontaneously hypertensive heart failure	-Collagen organization	Medeiros et al. [58]
				-Myocardial infarction	-Smad2/3 activation	Weis et al. [21]
					-TGF-β	Jahanyar et al. [59]
						Li et al. [28]
						Yan et al. [29]
			Cardiomyocyte hypertrophy	Spontaneously hypertensive rats	-p38 MAPK	Yan et al. [29]
					-TGF-β/Smad	
			Cardiomyocyte death	–	TLR4	Gorbe et al. [30]
		Lumican	Cardiac fibrosis	-Ischemia-reperfusion	-Collagen-cross-linking	Baba et al. [23]
				-Aortic banding	-MMP-9	Chen et al. [61]
				-Isoproterenol-induced cardiac fibrosis	-TGF-β-Smad3	Mohammadzadeh et al. [62]
						Engebretsen et al. [63]
		Osteoglycin	Cardiac fibrosis	-AngII-induced cardiac hypertrophy	-Cardiac fibroblasts proliferation	Van Aelst et al. [25]
				-Myocardial infarction	-TGF-β signaling	Petretto et al. [64]
				-Aortic banding	-Collagen maturation	Deckx et al. [66]
					-MMP-2	Voss et al. [65]
			Inflammation	AngII-induced cardiac hypertrophy	Pro-inflammatory cytokines and chemokines	Deckx et al. [66]
		Fibromodulin	Cardiomyocyte hypertrophy	Aortic banding	ERK1/2 signaling	Andenaes et al. [72]
		Podocan	Cardiomyocyte hypertrophy	Aortic banding	Wnt-pathway activity	Speidl et al. [73]

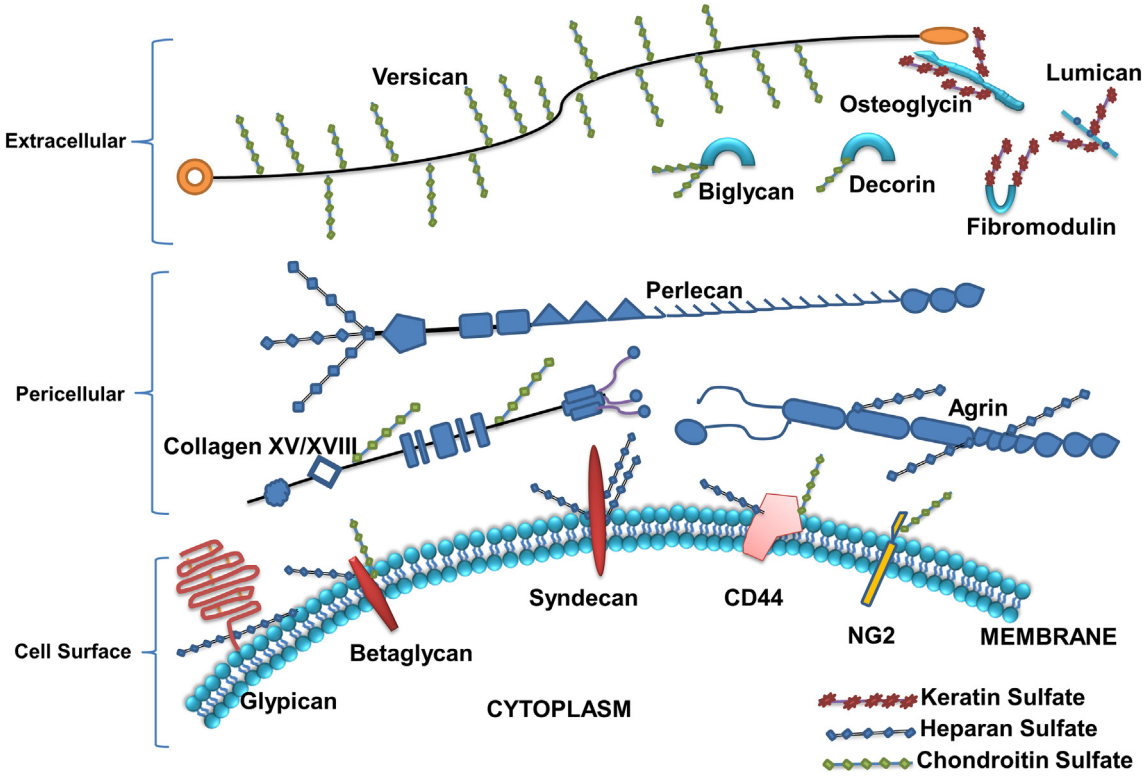

Fig. 1. Schematic representation of proteoglycans involved in cardiovascular remodeling.

The absence of Sdc1 or Sdc4 results in adverse cardiac remodeling after myocardial infarction (MI) by augmenting cardiac inflammation or suppressing cardiac apoptosis [11–14]. Sdc1 functions as a barrier against invading inflammatory cells through masking adhesion ligands on endothelial cells and competing inflammatory chemokines [11]. The loss of Sdc1 leads to increased cardiac inflammation and monocyte chemoattractant protein-1 expression after MI. Moreover, increased Sdc1 expression reduces cardiac inflammation by decreasing leukocyte-endothelia interactions [11]. Sdc1 or Sdc4 over-expression through injection of adenovirus containing Sdc1/Sdc4 gene in the infarcted myocardium is also of therapeutic benefit [12,13]. It improves post-MI cardiac remodeling by suppressing cardiac inflammation and reducing apoptosis through the p38 mitogen-activated protein kinase (MAPK) or extracellular signal-regulated kinase (ERK) pathways [12–14]. Mice deficient of Sdc4 demonstrate increased myocardial damage with enhanced apoptosis of cardiomyocytes after ischemia-reperfusion injury. ERK dephosphorylation promotes apoptosis, and Sdc4 activates p44-ERK to reduce the incidence of cell death [14]. In addition, increased Sdc4 expression by vibroacoustic transthoracic stimulation in mice post-MI could improve left ventricular (LV) function by downregulating the c-Jun N-terminal kinase (JNK)/ERK ratio and nuclear factor of activated T cell (NFAT) levels [15].

Sdc1 and Sdc4 are also essential mediators in cardiac remodeling post-MI by amplifying profibrotic signaling. Both Sdc1and Sdc4 contain HS chains, which could interact with various growth factors or receptors to modulate cardiac fibrosis [16,17]. The absence of Sdc1 or Sdc4 prevents infarct healing post-MI and results in cardiac dilatation or cardiac rupture [11,18]. Sdc4 is vital in granulation tissue formation post-MI. The differentiation of cardiac fibroblasts into myofibroblasts is defective in Sdc4-deficient mice [18]. Sdc1 loss in cardiac fibroblasts is associated with reduced activation of the Smad2 pathway [19]. By contrast, Sdc1 overexpression improves post-MI ventricular remodeling. Sdc1 augments fibrogenic responses by accentuating transforming growth factor-β (TGF-β) and angiotensin II (AngII) mediated Smad2 phosphorylation and connective tissue growth factor (CTGF) expression [19]. The inhibition of HS chains by protamine prevents the induction of CTGF and collagen I by Sdc1 after AngII stimulation [19,20].

2.1.2. Small leucine-rich proteoglycans (SLRPs): biglycan, decorin, lumican and osteoglycin

SLRPs are proteoglycans with a relatively small protein core of 36–42 kDa. They are characterized by a central region constituted by leucine-rich repeats [7]. SLRPs, particularly biglycan, decorin, lumican and osteoglycin, are of significant importance in ischemia-induced cardiac fibrosis. They are all elevated in models of MI or ischemia/reperfusion. Mice that lack any of these SLRPs and subjected to ischemia tend to exhibit less organization in mature scars or ventricular rupture [21–25].

Biglycan and decorin are members of class I SLRPs, which contain CS or DS chains and share the most structural homology. Both biglycan and decorin have been shown to interact with collagens and elastin via its core protein or GAG chains to promote collagen stability [26]. Decorin has also been suggested to reduce the aggregation of fibrils into fibers and fiber bundles, thus increasing the modulus and tensile strength of collagen gels [27]. Besides, decorin inhibits fibroblast transformation into myofibroblasts and attenuates activated TGF-β signaling to prevent adverse fibrosis by decreasing phosphorylated Smad2 expression and increasing Smad6 expression [28,29]. Furthermore, biglycan and decorin have been shown to protect cardiomyocytes against hypoxia/reoxygeneration injury by increasing endothelial nitric oxide (NO) synthase [30]. Biglycan also modulates the necrosis, apoptosis and autophagy of cardiomyocytes by activating the Toll-like receptor 4 (TLR4) pathways and its downstream mediators [31].

Both lumican and osteoglycin are SLRPs modified with KS. The expression of lumican is increased in ischemic and reperfused rat hearts compared with control rat hearts. Lumican is localized in proliferated collagen fibers of the infarct lesion and mainly contributes to collagen fiber assembly in fibrotic lesions [23]. Osteoglycin, also referred as mimecan, is essential for maintaining the integrity of the cardiac ECM

after MI [25]. Osteoglycin stabilizes the infarct scar tissue by bridging with collagen fibrils to create non-enzymatic collagen cross-links [32]. The upregulation of osteoglycin by adenovirus alleviates adverse collagen deposition and blunts cardiac dysfunction after MI [25].

2.1.3. Other proteoglycans: perlecan, agrin, NG2, CD44, and collagen XVIII

Perlecan and agrin belong to the group of pericellular proteoglycans. Both of them contain HS chains and have a homologous multimodular structural organization [7]. The expression of perlecan is increased after MI. Perlecan interacts with type IV collagen and promotes growth factor-receptor interactions to affect ECM remodeling [33]. Perlecan is also induced by basic fibroblast growth factor (bFGF) to promote ischemic myocardial angiogenesis via focal adhesion kinase (FAK) and the p38 MAPK pathway. The up-regulation of perlecan by myocardial injection of bFGF has been shown to reduce the size of infarcted myocardium and improve cardiac function [34]. Administration of agrin may have therapeutic potential in MI by promoting cardiac regeneration. Recombinant agrin could trigger cardiomyocyte proliferation, and mice deficient of agrin in cardiac mesoderm induce cardiac maturation. By binding to the dystrophin glycoprotein complex (DGC) through α-dystroglycan, agrin reduces the stability of DGC and activates Yap and ERK signaling, leading to cardiomyocyte division. Intramyocardial injection of agrin facilitates cardiomyocyte cell cycle re-entry in myocardium adjacent to the infarcted area and improves cardiac function [35].

Both nerve glial antigen 2 (NG2) and cluster of differentiation 44 (CD44) are cell surface proteoglycans [7]. NG2 typically presents in embryonic cardiac myocytes and is upregulated in the infarct border zone. Mice that lack NG2 manifest with more interstitial fibrosis and cardiac dysfunction compared with wild type (WT) mice [36]. CD44 functions as the main receptor for HA and transduces intracellular cascades to modulate inflammation and fibrosis. The expression of CD44 is substantially upregulated in infarcted myocardium and expressed in infiltrating leukocytes. A lack of CD44 aggravates neutrophil and macrophage infiltration and promotes the production of cytokines and chemokines in the infarcted myocardium [37]. The CD44-HA interaction impaired by a matrix metalloproteinase-12 (MMP-12) inhibitor prolongs inflammation and worsens cardiac function [38]. CD44 also triggers the proliferation of cardiac fibroblasts and promotes TGF-β signaling [37,39]. CD44-HA interaction may also be linked to cardiac remodeling through enhancing Na^+/H^+ exchanger isoform-1 (NHE1) activity [40].

Collagen XVIII (ColXVIII), which contains HS chains, harbors structural features of collagen and proteoglycan. Proteolytic cleavage of colXVIII generates endostatin. The expressions of colXVIII and endostatin are elevated in cardiomyocytes of the infarcted area and isolated rat neonatal cardiomyocytes under hypoxic stimuli. Endostatin neutralization elevates multiple MMP activities, thus leading to adverse LV remodeling and impaired heart function. It indicates that colXVIII may suppress adverse cardiac remodeling post-MI [41].

2.2. Proteoglycans exacerbating pathological cardiac remodeling of myocardial ischemia

Proteoglycans, including betaglycan and versican, are linked to adverse cardiac remodeling post-MI by affecting cardiomyocyte apoptosis, inflammation and fibrosis [42–44].

Betaglycan, also referred to as TGFβ type III receptor, is a type of transmembrane proteoglycan that acts as a co-receptor for the TGFβ superfamily. Increased betaglycan expression in cardiomyocytes promotes cell apoptosis and cardiac fibrosis. Cardiac betaglycan transgenic mice present with an enlarged infarct size and augmented cardiomyocyte apoptosis through activation of p38 signaling [42]. It has been demonstrated that simvastatin upregulates betaglycan expression in cardiac fibroblasts to alleviate fibrosis by inhibiting ERK1/2 and JNK signaling, whereas silencing cardiac betaglycan promotes fibrosis and improves cardiac function in MI [43].

Versican is a large chondroitin sulfate proteoglycan located in the extracellular matrix and is upregulated at the infarct borders accompanied by increased infiltration of CD45+ cells [44]. Mice deficient of versican show a reduced injured wall thickness, less infiltration of cardiac fibroblasts and collagen deposition. Increased versican expression in mice leads to adverse remodeling after MI [44].

3. Proteoglycans in pressure-overload related cardiac remodeling

3.1. Proteoglycans promoting favorable cardiac remodeling after pressure overload

3.1.1. Syndecans: Sdc4

Sdc4 is an important modulator in pressure-overload induced cardiac remodeling. The lack of Sdc4 leads to cardiomegaly and heart dysfunction in response to aortic banding [45]. During different stages of the disease, Sdc4 demonstrates various functions in cardiomyocytes, immune cells and fibroblasts.

Sdc4 is present in costameres and the Z-disc of cardiomyocytes [46], which is the crucial site of mechano-sensing and signal transduction across the membrane [47]. This special location makes it a very possible candidate related to cardiomyocyte hypertrophy. Compared with respective sham-operated mice, the Sdc4 expression is elevated in mice that undergo aortic banding [48]. Further studies have shown that Sdc4 is a mechanotransducer for calcineurin-NFAT signaling. Calcineurin is a calcium/calmodulin-dependent protein phosphatase, and could dephosphorylate transcription factors of the NFAT family, leading to their translocation to the nucleus and ultimately activating hypertrophic genes [49]. Mechanical stretch could trigger significant calcineurin-dependent NFAT activation in WT cardiomyocytes and substantially lower the level of NFAT activation in Sdc4−/− cardiomyocytes [45,50]. It seems that Sdc4 is an important modulator in cardiac hypertrophy by regulating the calcineurin-NFAT pathway. Moreover, Sdc4 knockout mice subjected to aortic banding also exhibit a reduced capillary density with a decrease in protein kinase C alpha expression. These findings indicate that Sdc4 is essential for cardiac hypertrophy by regulating adaptive angiogenesis [51].

In mice subjected to aortic banding, all four syndecans participate in hypertrophic remodeling by influencing inflammatory pathways, particularly Sdc4 [52]. Cardiac expression of Sdc4 is induced by inflammatory cytokines to affect immune cell infiltration. In Sdc4 knock-out mice, T-cell specific markers are reduced, which suggests impaired inflammation [53]. Pressure overload also increases the cardiac levels of Sdc4 fragment, which indicates that Sdc4 is shed during hypertrophic remodeling. Neonatal cardiomyocytes cultured in conditioned medium that contains shed Sdc4 ectodomains induce the expression of inflammatory cytokines and receptors. Inflammatory cytokines could also upregulate enzymes to mediate Sdc4 shedding. It implies that Sdc4 shedding may be central to the inflammatory process in hypertrophic remodeling [54].

Sdc4 also promotes collagen cross-linking and myocardial stiffening in the pressure-overloaded heart. Sdc4 co-localizes with integrins in fibroblast focal adhesions and function cooperatively with integrins to initiate mechanochemical signaling [55]. Studies have shown that cardiac fibroblasts isolated from Sdc4−/− mice demonstrate reduced numbers of focal adhesions and impaired differentiation into myofibroblasts. Moreover, the overexpression of Sdc4 increases myofibroblast transformation [56]. Sdc4 is engaged in the differentiation of cardiac fibroblasts into myofibroblasts and the production of ECM through the calcineurin/NFAT pathway [57]. Further studies have shown that it is not the total collagen content but rather collagen cross-linking that is affected by Sdc4 [56].

In general, Sdc4 plays a protective role in pressure-overload conditions to accelerate compensated cardiomyocyte hypertrophy. Nevertheless, since Sdc4 promotes cardiac fibrosis, the diastolic function of the pressure-overloaded heart may be impaired in the long run.

3.2. Proteoglycans mitigating pathological cardiac remodeling after pressure overload

3.2.1. SLRPs: decorin, lumican and osteoglycin

In spontaneously hypertensive heart failure (SHHF) rats, the expression of decorin is gradually enriched during its progression to heart failure, along with an increased ratio of type I to type III collagen. Decorin has been shown to bind to collagen, which alters the organization and crosslinks of fibrils [58]. Human cardiac fibroblasts cultured with exogenous decorin demonstrate decreased collagen production in response to TGF-β [59]. Moreover, gene delivery by r-AAV vector to increase decorin expression substantially mitigates the LV dysfunction in hypertensive rats [29]. These findings indicate that decorin may attenuate the effects of adverse remodeling.

Lumican controls cardiomyocyte growth by regulating ECM. Lumican deficient mice exhibit an enlarged heart with an increased cardiomyocyte size and alteration of other ECM components [60]. After isoproterenol infusion or transverse aortic constriction (TAC), lumican-null mice show significantly impaired systolic function and severe ventricular fibrosis [61,62]. Cyclic mechanical stretch and IL-β stimulation of cardiac fibroblasts has been suggested to increase the expression and release of lumican. Cardiac fibroblasts stimulated with recombinant glycosylated lumican show increased expression of Collagen 1A2 and lysyl oxidase, which thus facilitates collagen cross-linking. Furthermore, lumican may downregulate the amount of collagen by decreasing the activity of MMP-9 [63]. These results suggest that lumican can change both the quantity and quality of collagen. Interestingly, lumican also promotes the expression of TGF-β1 and the phosphorylation of Smad3 in cardiac fibroblasts [63], thus indicating that lumican may impact cardiac fibrosis, in part, through the TGF-β pathway.

Osteoglycin is linked to cardiac hypertrophy in a genome wide analysis of the rat heart. Patients with aortic stenosis and elevated left ventricular mass (LVM) present with an increased expression of osteoglycin [64]. Compared with WT mice, mice that lack osteoglycin manifest a significant attenuation in the LVM response with the stimulation of AngII [64]. In the TAC model, osteoglycin deficiency leads to impaired heart function, ventricular dilatation and fibrosis [65]. A further in vitro study indicates that osteoglycin could reduce cardiac fibroblast proliferation and inhibit the TGF-β pathway. Macrophages derived from osteoglycin null mice exhibit higher levels of pro-inflammatory cytokines and chemokines. The absence of osteoglycin leads to diastolic dysfunction resulting from cardiac inflammation and fibrosis [66].

3.2.2. Collagen XV (ColXV)

ColXV is a nonfibrillar collagen composed of a highly interrupted collagenous domain flanked by large globular domains and CS chains [67]. ColXV belongs to the family of pericellular proteoglycans, which are closely associated with the surface of many cell types via integrins or other receptors [7]. The loss of ColXV in mice triggers cardiac dysfunction, which manifests as a blunted contractile response to stimulation with isoproterenol in isolated and perfused hearts [68]. Moreover, ColXV is essential for the organization of fibrillar collagen matrix in cardiac muscle, and the lack of ColXV increases myocardial stiffness [68]. A further in vivo study indicates that in response to experimental hypertension, the expression of ColXV is increased in the left ventricles of wild-type mice [68]. Moreover, mice that lack ColXV show less induction of natriuretic peptide mRNAs and qualitatively different fibrotic lesions compared with WT mice in the condition of hypertension. Mice absent of ColXV share similar hypertrophic responses with WT mice; however, the ECM remodeling in the LV is abnormal with an increased Collagen I/III mRNA ratio [68]. These findings indicate that ColXV mainly affects the composition of the ECM and subsequently influences the heart function.

3.3. Proteoglycans pending further clarification in pressure-overload related cardiac remodeling

Both betaglycan and glypican-6 belong to the cell surface proteoglycans. Betaglycan is significantly increased in patients' hypertrophic heart tissue and mediates pressure-overload induced cardiac hypertrophy through activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) [69]. Glypican-6 is upregulated in mice subjected to aortic banding from hypertrophic remodeling to heart failure and correlated with the severity of cardiac dysfunction. Some studies indicate that glypican-6 regulates cardiomyocyte growth via ERK signaling [70]. However, further investigations are required to determine the potential involvement of betaglycan and glypican-6 in the prevention or treatment of pressure-overload provoked cardiac dysfunction.

Biglycan, fibromodulin and podocan belong to the family of SLRPs, and are all upregulated in mice subjected to TAC [71–73]. Mice that lack biglycan and undergo TAC demonstrate attenuated ventricular fibrosis and improved heart function [71]. However, the loss of biglycan impairs cardiac function during AngII induced heart failure [74]. More research is needed to confirm and reveal the underlying mechanism of biglycan during the process of pressure-overload induced cardiac remodeling. Compared with WT mice, fibromodulin knock-out mice that undergo TAC develop mildly exacerbated hypertrophic remodeling with upregulated ERK1/2 signaling [72]. A deficiency in podocan promotes cardiac hypertrophy in the TAC model with increased Wnt-pathway activation [73]. Nevertheless, whether the upregulation of fibromodulin or podocan could be used to alleviate pressure-overload induced cardiac dysfunction has not been elucidated.

4. Future perspectives and conclusions

An increasing body of evidence shows that proteoglycans are crucial modulators in cardiac remodeling. Nevertheless, treatment options that target specific proteoglycans in cardiovascular diseases are scarce and insufficient (Table 2). The implementation of novel therapeutic methods associated with proteoglycans may shed new light on the management of cardiovascular diseases.

Direct intramyocardial administration of agrin has been demonstrated to promote cardiac regeneration in mice after MI [48], which highlights the therapeutic potential of proteoglycans in cardiac repair. Perlecan is homologous to agrin, and the upregulation of perlecan by injecting bFGF could reduce the size of infarcted myocardium [34]. It is

Table 2
Specific proteoglycans in the treatment of cardiovascular diseases.

Proteoglycans	Diseases	Methods	References
Sdc1	Myocardial infarction (rat)	Intramyocardial injection of adenovirus-carrying Sdc1 cDNA	Lei et al. [13]
Sdc4	Myocardial infarction (rat)	Intramyocardial injection of adenovirus-carrying Sdc4 gene	Xie et al. [12]
	Myocardial infarction (mouse)	Increased Sdc4 expression by vibroacoustic transthoracic stimulation	Uryash et al. [15]
Perlecan	Myocardial infarction (rat)	Intramyocardial injection of bFGF	Fu et al. [34]
Agrin	Myocardial infarction (mouse)	Intramyocardial injection of agrin	Bassat et al. [35]
Betaglycan	Myocardial infarction (mouse)	Intramyocardial injection of lentivirus with betaglycan short hairpin RNA	Sun et al. [43]
Decorin	Myocardial infarction (mouse)	Adenoviral vectors encoding human decorin injected into the hindlimbs	Li et al. [28]
	Spontaneous hypertension (rat)	Intravenous injection of recombinant adeno-associated viral vector containing decorin gene	Yan et al. [29]
Osteoglycin	Myocardial infarction (mouse)	Intravenous injection of adenovirus-overexpressing osteoglycin	Van et al. [25]

reasonable to suspect that intramyocardial administration of perlecan may also be effective in the treatment of MI.

Proteoglycans could be upregulated or downregulated in animals via delivering viral vectors. Intramyocardial or intravenous injection of adenovirus to overexpress proteoglycans that are beneficial for cardiac remodeling post-MI is therapeutic [12,13,25,28]. Moreover, silencing proteoglycans that are detrimental for cardiac remodeling is also effective in the treatment of MI [43]. Intravenous injection of recombinant adeno-associated viral vectors that contain decorin into spontaneously hypertensive rats has also been shown to be effective in reducing collagen accumulation and improving cardiac function [29]. Thus, delivering viral vectors to regulate the expression of other proteoglycans may also be effective in the treatment of cardiovascular diseases.

Decellularized myocardial matrix hydrogels delivered via transendocardial injection have shown substantial promise to reverse adverse cardiovascular remodeling post-MI [75,76]. However, these matrix hydrogels are derived from healthy animal heart tissues. They contain components that may not favor cardiac remodeling or lack proteoglycans that are critical for cardiac function improvement. Therefore, future matrix hydrogels containing proteoglycans that have been verified to be beneficial in cardiac remodeling might be a novel therapy for cardiovascular diseases.

As proteoglycans are synthesized and degraded by various enzymes, approaches that upregulate or suppress relative enzymes to regulate the quantity and quality of ECM may also be promising. ADAMTS4 (a disintegrin and metalloprotease with thrombospondin motifs) has been demonstrated to degrade proteoglycans, including versican, whereas pentosan polysulfate (PPS) inhibits the function of ADAMTS4. Subcutaneous injection of PPS in rats undergoing aortic banding improves cardiac function by downregulating ADAMTS4 [77]. Heparanase specifically decomposes HS chains, and it is upregulated in ventricular hypertrophy [78]. The inhibition of heparanase activity may hold promise in reversing adverse cardiac remodeling. Proteoglycans that contain CS chains, such as decorin and biglycan, play significant roles in the process of heart failure. Arylsulfatase B could degrade CS chains, and intravenous administration of this enzyme is effective at preventing and improving cardiac dysfunction in rats subjected to TAC or isoprenaline infusion [79].

In conclusion, proteoglycans could modulate cardiac remodeling in antecedent diseases leading to heart failure. Novel therapeutic methods associated with proteoglycans may provide new opportunities for further improvement in the prognosis of cardiovascular diseases.

Funding and acknowledgments

This work was supported by grants from the Provincial and Ministry Joint Major Projects of National Health Commission of China (WKJ-ZJ-1703 to Mei-xiang Xiang), and the National Natural Science Foundation of China (No. 81470384 and No. 81670259 to Mei-xiang Xiang).

Disclosure

Dr. Mei-xiang Xiang was granted by the Provincial and Ministry Joint Major Projects of National Health Commission of China (WKJ-ZJ-1703), and the National Natural Science Foundation of China (No. 81470384 and No. 81670259). The remaining authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.125.

References

[1] C.W. Yancy, M. Jessup, B. Bozkurt, et al., ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Failure Society of America, J. Card. Fail. 23 (2017) 628–651.
[2] P. Ponikowski, A.A. Voors, S.D. Anker, et al., ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. J. Heart Fail. 18 (2016) 891–975.
[3] M.R. Zile, C.F. Baicu, Biomarkers of diastolic dysfunction and myocardial fibrosis: application to heart failure with a preserved ejection fraction, J. Cardiovasc. Transl. Res. 6 (2013) 501–515.
[4] G. Heusch, P. Libby, B. Gersh, et al., Cardiovascular remodelling in coronary artery disease and heart failure, Lancet 383 (2014) 1933–1943.
[5] F. Fares, The role of O-linked and N-linked oligosaccharides on the structure-function of glycoprotein hormones: development of agonists and antagonists, Biochim. Biophys. Acta 1760 (2006) 560–567.
[6] S. Bousseau, L. Vergori, R. Soleti, G. Lenaers, M.C. Martinez, R. Andriantsitohaina, Glycosylation as new pharmacological strategies for diseases associated with excessive angiogenesis, Pharmacol. Ther. 191 (2018 Nov) 92–122.
[7] R.V. Iozzo, L. Schaefer, Proteoglycan form and function: a comprehensive nomenclature of proteoglycans, Matrix Biol. J. Int. Soc. Matrix Biol. 42 (2015) 11–55.
[8] I. Strate, F. Tessadori, J. Bakkers, Glypican4 promotes cardiac specification and differentiation by attenuating canonical Wnt and Bmp signaling, Development (Cambridge) 142 (2015) 1767–1776.
[9] C.Y. Fears, A. Woods, The role of syndecans in disease and wound healing, Matrix Biol. J. Int. Soc. Matrix Biol. 25 (2006) 443–456.
[10] A.V. Finsen, P.R. Woldbaek, J. Li, et al., Increased syndecan expression following myocardial infarction indicates a role in cardiac remodeling, Physiol. Genomics 16 (2004) 301–308.
[11] D. Vanhoutte, M.W. Schellings, M. Gotte, et al., Increased expression of syndecan-1 protects against cardiac dilatation and dysfunction after myocardial infarction, Circulation 115 (2007) 475–482.
[12] J. Xie, J. Wang, R. Li, et al., Syndecan-4 over-expression preserves cardiac function in a rat model of myocardial infarction, J. Mol. Cell. Cardiol. 53 (2012) 250–258.
[13] J. Lei, S. Xue, W. Wu, et al., Sdc1 overexpression inhibits the p38 MAPK pathway and lessens fibrotic ventricular remodeling in MI rats, Inflammation 36 (2013) 603–615.
[14] F. Echtermeyer, T. Harendza, S. Hubrich, et al., Syndecan-4 signalling inhibits apoptosis and controls NFAT activity during myocardial damage and remodelling, Cardiovasc. Res. 92 (2011) 123–131.
[15] A. Uryash, J.A. Adams, Wearable vibroacoustic transthoracic stimulation (VATS) provides cardioprotection by syndecan-4 mechanosensor regulation of NFAT, JNK/ERK in rats after myocardial infarction, Circulation 136 (2017).
[16] H. Koppel, B.A. Yard, M. Christ, M. Wehling, F.J. van der Woude, Modulation of angiotensin II-mediated signalling by heparan sulphate glycosaminoglycans, Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transplant Assoc. Eur. Ren. Assoc. 18 (2003) 2240–2247.
[17] L. Li, E.L. Chaikof, Mechanical stress regulates syndecan-4 expression and redistribution in vascular smooth muscle cells, Arterioscler. Thromb. Vasc. Biol. 22 (2002) 61–68.
[18] Y. Matsui, M. Ikesue, K. Danzaki, et al., Syndecan-4 prevents cardiac rupture and dysfunction after myocardial infarction, Circ. Res. 108 (2011) 1328–1339.
[19] M.W.M. Schellings, D. Vanhoutte, G.C. Van Almen, et al., Syndecan-1 amplifies angiotensin II-induced cardiac fibrosis, Hypertension 55 (2010) 249–256.
[20] N.G. Frangogiannis, Syndecan-1: a critical mediator in cardiac fibrosis, Hypertension 55 (2010) 233–235.
[21] S.M. Weis, S.D. Zimmerman, M. Shah, et al., A role for decorin in the remodeling of myocardial infarction, Matrix Biol. J. Int. Soc. Matrix Biol. 24 (2005) 313–324.
[22] D. Westermann, J. Mersmann, A. Melchior, et al., Biglycan is required for adaptive remodeling after myocardial infarction, Circulation 117 (2008) 1269–1276.
[23] H. Baba, T. Ishiwata, E. Takashi, G. Xu, G. Asano, Expression and localization of lumican in the ischemic and reperfused rat heart, Jpn. Circ. J. 65 (2001) 445–450.
[24] L.N.L.C. Van Aelst, M. Swinnen, M. Schellings, et al., Mimecan is an essential regulator of cardiac extracellular matrix integrity after myocardial infarction, Eur. Heart J. 31 (2010) 6.
[25] L.N.L. Van Aelst, S. Voss, P. Carai, et al., Osteoglycin prevents cardiac dilatation and dysfunction after myocardial infarction through infarct collagen strengthening, Circ. Res. 116 (2015) 425–436.
[26] M.V. Nastase, M.F. Young, L. Schaefer, Biglycan: a multivalent proteoglycan providing structure and signals, J. Histochem. Cytochem. Off. J. Histochem. Soc. 60 (2012) 963–975.
[27] S.P. Reese, C.J. Underwood, J.A. Weiss, Effects of decorin proteoglycan on fibrillogenesis, ultrastructure, and mechanics of type I collagen gels, Matrix Biol. J. Int. Soc. Matrix Biol. 32 (2013) 414–423.
[28] L. Li, H. Okada, G. Takemura, et al., Postinfarction gene therapy with adenoviral vector expressing decorin mitigates cardiac remodeling and dysfunction, Am. J. Physiol. Heart Circ. Physiol. 297 (2009) H1504–H1513.
[29] W. Yan, P. Wang, C.X. Zhao, J. Tang, X. Xiao, D.W. Wang, Decorin gene delivery inhibits cardiac fibrosis in spontaneously hypertensive rats by modulation of transforming growth factor-beta/Smad and p38 mitogen-activated protein kinase signaling pathways, Hum. Gene Ther. 20 (2009) 1190–1200.
[30] A. Gorbe, A. Szunyoh, T. Csont, E. Bereczki, M. Santha, P. Ferdinandy, Biglycan and decorin protect cardiomyocytes against hypoxia-reoxygenation injury by an NO-dependent mechanism, Eur. J. Heart Fail. Suppl. 8 (2009) ii334–ii335.
[31] R. Gaspar, M. Pipicz, F. Hawchar, et al., The cytoprotective effect of biglycan core protein involves toll-like receptor 4 signaling in cardiomyocytes, J. Mol. Cell. Cardiol. 99 (2016) 138–150.
[32] G. Christensen, K.M. Herum, I.G. Lunde, Sweet, yet underappreciated: proteoglycans and extracellular matrix remodeling in heart disease, Matrix Biol. (2018) (in press).

[33] M. Nakahama, T. Murakami, S. Kusachi, et al., Expression of perlecan proteoglycan in the infarct zone of mouse myocardial infarction, J. Mol. Cell. Cardiol. 32 (2000) 1087–1100.
[34] Y. Fu, X.H. Liu, X.M. Zhao, et al., Perlecan participates in the protection of ischemic myocardium induced by basic fibroblast growth factor: experiment with rats, Natl. Med. J. China 87 (2007) 1857–1861.
[35] E. Bassat, Y.E. Mutlak, A. Genzelinakh, et al., The extracellular matrix protein agrin promotes heart regeneration in mice, Nature 547 (2017) 179–184.
[36] J. Offerhaus, P. Rainer, P. Andersen, et al., NG2+ cells protect against cardiac remodeling and failure after myocardial infarction in mice, Circulation (2015) 132.
[37] P. Huebener, T. Abou-Khamis, P. Zymek, et al., CD44 is critically involved in infarct healing by regulating the inflammatory and fibrotic response, J. Immunol. 180 (2008) 2625–2633.
[38] R.P. Iyer, N.L. Patterson, F.A. Zouein, et al., Early matrix metalloproteinase-12 inhibition worsens post-myocardial infarction cardiac dysfunction by delaying inflammation resolution, Int. J. Cardiol. 185 (2015) 198–208.
[39] L.W. Yang, D.Z. Qin, E. James, et al., CD44 deficiency in mice protects the heart against angiotensin II-induced cardiac fibrosis, Shock (Augusta, GA) (2018) (in press).
[40] M. Suleiman, N. Abdulrahman, H. Yalcin, F. Mraiche, The role of CD44, hyaluronan and NHE1 in cardiac remodeling, Life Sci. 209 (2018) 197–201.
[41] K. Isobe, K. Kuba, Y. Maejima, J. Suzuki, S. Kubota, M. Isobe, Inhibition of endostatin/collagen XVIII deteriorates left ventricular remodeling and heart failure in rat myocardial infarction model, Circ J 74 (2010) 109–119.
[42] F. Sun, X. Li, W.Q. Duan, et al., Transforming growth factor-beta receptor III is a potential regulator of ischemia-induced cardiomyocyte apoptosis, J. Am. Heart Assoc. 6 (2017), e005357.
[43] F. Sun, W. Duan, Y. Zhang, et al., Simvastatin alleviates cardiac fibrosis induced by infarction via up-regulation of TGF-beta receptor III expression, Br. J. Pharmacol. 172 (2015) 3779–3792.
[44] C. Mjaatvedt, T. Burns, P. Escobar, Y. Ansarizadeh, C. Le Saux, Adverse cardiac remodeling mediated by the altered expression of versican, FASEB J. 28 (1 SUPPL) (2014) 1.
[45] A.V. Finsen, I.G. Lunde, I. Sjaastad, et al., Syndecan-4 is essential for development of concentric myocardial hypertrophy via stretch-induced activation of the calcineurin-NFAT pathway, PLoS One 6 (2011), e28302.
[46] W.B. Vanwinkle, M.B. Snuggs, E.L. De Hostos, L.M. Buja, A. Woods, J.R. Couchman, Localization of the transmembrane proteoglycan syndecan-4 and its regulatory kinases in costameres of rat cardiomyocytes: a deconvolution microscopic study, Anat. Rec. 268 (2002) 38–46.
[47] W.G. Pyle, R.J. Solaro, At the crossroads of myocardial signaling: the role of Z-discs in intracellular signaling and cardiac function, Circ. Res. 94 (2004) 296–305.
[48] M.E. Strand, K.M. Herum, Z.A. Rana, et al., Innate immune signaling induces expression and shedding of the heparan sulfate proteoglycan syndecan-4 in cardiac fibroblasts and myocytes, affecting inflammation in the pressure-overloaded heart, FEBS J. 280 (2013) 2228–2247.
[49] G.R. Crabtree, E.N. Olson, NFAT signaling: choreographing the social lives of cells, Cell 109 (Suppl) (2002) S67–S79.
[50] I.G. Lunde, G. Florholmen, A.V. Finsen, et al., The Z-disc proteoglycan syndecan-4 regulates mechanical stress-induced calcineurin-NFAT signaling in cardiomyocytes, Circulation (2011) 124.
[51] G. Li, J. Xie, J. Chen, et al., Syndecan-4 deficiency accelerates the transition from compensated hypertrophy to heart failure following pressure overload, Cardiovasc Pathol 28 (2017) 74–79.
[52] I.G. Lunde, V. Almaas, M.E. Strand, et al., Myocardial levels of the syndecan proteoglycan family are associated with inflammation, arrhythmogenesis and septal function in obstructive hypertrophic cardiomyopathy, Eur. J. Heart Fail. 16 (2014) 111.
[53] M.E. Strand, K.M. Herum, Z.A. Rana, et al., The adhesion site transmembrane proteoglycan syndecan-4; an integrator of pro-hypertrophic and pro-inflammatory signaling in the heart? Circulation (2012) 126.
[54] M.E. Strand, B. Skrbic, I. Sjaastad, et al., Syndecan-4 shedding is involved in the innate immune response of the heart to LPS challenge and pressure overload, Eur. J. Heart Fail. 16 (2014) 213.
[55] R.M. Bellin, J.D. Kubicek, M.J. Frigault, et al., Defining the role of syndecan-4 in mechanotransduction using surface-modification approaches, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 22102–22107.
[56] K.M. Herum, I.G. Lunde, B. Skrbic, et al., Syndecan-4 is a key determinant of collagen cross-linking and passive myocardial stiffness in the pressure-overloaded heart, Cardiovasc. Res. 106 (2015) 217–226.
[57] K.M. Herum, I.G. Lunde, B. Skrbic, et al., Syndecan-4 signaling via NFAT regulates extracellular matrix production and cardiac myofibroblast differentiation in response to mechanical stress, J. Mol. Cell. Cardiol. 54 (2013) 73–81.
[58] D.M. Medeiros, S.G. Velleman, B.B. Jarrold, L.J. Shiry, M.J. Radin, S.A. McCune, Ontogeny of enhanced decorin levels and distribution within myocardium of failing hearts, Connect. Tissue Res. 43 (2002) 32–43.
[59] J. Jahanyar, D.L. Joyce, R.E. Southard, et al., Decorin-mediated transforming growth factor-β inhibition ameliorates adverse cardiac remodeling, J. Heart Lung Transplant. 26 (2007) 34–40.
[60] L.E. Dupuis, M.G. Berger, S. Feldman, et al., Lumican deficiency results in cardiomyocyte hypertrophy with altered collagen assembly, J. Mol. Cell. Cardiol. 84 (2015) 70–80.
[61] S.W. Chen, Y.C. Tung, S.M. Jung, et al., Lumican-null mice are susceptible to aging and isoproterenol-induced myocardial fibrosis, Biochem. Biophys. Res. Commun. 482 (2017) 1304–1311.
[62] N. Mohammadzadeh, I.G. Lunde, K. Andenas, et al., Lack of the extracellular matrix proteoglycan lumican in mice exacerbates left ventricular dilatation and contractile dysfunction upon pressure overload, Eur. Heart J. 38 (2017) 1248.
[63] K.V.T. Engebretsen, I.G. Lunde, M.E. Strand, et al., Lumican is increased in experimental and clinical heart failure, and its production by cardiac fibroblasts is induced by mechanical and proinflammatory stimuli, FEBS J. 280 (2013) 2382–2398.
[64] E. Petretto, R. Sarwar, I. Grieve, et al., Integrated genomic approaches implicate osteoglycin (Ogn) in the regulation of left ventricular mass, Nat. Genet. 40 (2008) 546–552.
[65] S. Voss, H.M. Nef, S. Szardien, et al., Osteoglycin deficiency leads to maladaptive remodeling and severe cardiac dysfunction in a mouse model of cardiac hypertrophy, Eur. Heart J. 33 (2012) 342.
[66] S. Deckx, W. Heggermont, P. Carai, et al., Osteoglycin prevents the development of age-related diastolic dysfunction during pressure overload by reducing cardiac fibrosis and inflammation, Matrix Biol. 66 (2018) 110–124.
[67] M. Hurskainen, F. Ruggiero, P. Hagg, T. Pihlajaniemi, P. Huhtala, Recombinant human collagen XV regulates cell adhesion and migration, J. Biol. Chem. 285 (2010) 5258–5265.
[68] K. Rasi, J. Piuhola, M. Czabanka, et al., Collagen XV is necessary for modeling of the extracellular matrix and its deficiency predisposes to cardiomyopathy, Circ. Res. 107 (2010) 1241–1252.
[69] J. Lou, D. Zhao, L.L. Zhang, et al., Type III transforming growth factor-beta receptor drives cardiac hypertrophy through beta-arrestin2-dependent activation of calmodulin-dependent protein kinase II, Hypertension 68 (2016) 654–666.
[70] A.O. Melleby, M.E. Strand, A. Romaine, et al., The heparan sulfate proteoglycan glypican-6 is upregulated in the failing heart, and regulates cardiomyocyte growth through ERK1/2 signaling, PLoS One 11 (2016), e0165079.
[71] N. Beetz, C. Rommel, T. Schnick, et al., Ablation of biglycan attenuates cardiac hypertrophy and fibrosis after left ventricular pressure overload, J. Mol. Cell. Cardiol. 101 (2016) 145–155.
[72] K. Andenaes, I.G. Lunde, N. Mohammadzadeh, et al., The extracellular matrix proteoglycan fibromodulin is upregulated in clinical and experimental heart failure and affects cardiac remodeling, PLoS One 13 (2018), e0201422.
[73] W.S. Speidl, L. Shenje, J.J. Badimon, D.J. Schneider, P. Klotman, R. Hutter, Deficiency in the novel small leucin-rich repeat protein podocan promotes pressure load-induced cardiac hypertrophy, Circulation 128 (2013).
[74] D. Westermann, P.M. Becher, D. Lindner, J.W. Fischer, C. Tschoepe, Biglcan is beneficial in angiotensin II induced heart failure by preventing cardiac inflammation and remodeling improving LV function and mortality by preventing transdifferentiation of myofibroblasts, Eur. Heart J. 34 (2013) 773.
[75] J.M. Singelyn, P. Sundaramurthy, T.D. Johnson, et al., Catheter-deliverable hydrogel derived from decellularized ventricular extracellular matrix increases endogenous cardiomyocytes and preserves cardiac function post-myocardial infarction, J. Am. Coll. Cardiol. 59 (2012) 751–763.
[76] R.M. Wang, K.L. Christman, Decellularized myocardial matrix hydrogels: in basic research and preclinical studies, Adv. Drug Deliv. Rev. 96 (2016) 77–82.
[77] M. Vistnes, J.M. Aronsen, I.G. Lunde, I. Sjaastad, C.R. Carlson, G. Christensen, Pentosan polysulfate decreases myocardial expression of the extracellular matrix enzyme ADAMTS4 and improves cardiac function in vivo in rats subjected to pressure overload by aortic banding, PLoS One 9 (2014), e89621.
[78] T. Ishiguro-Oonuma, M. Suemoto, M. Okada, et al., Aberrant gene expression of heparanase in ventricular hypertrophy induced by monocrotaline in rats, J. Vet. Med. Sci. 78 (2016) 499–503.
[79] R.R. Zhao, M. Ackers-Johnson, J. Stenzig, et al., Targeting chondroitin sulfate glycosaminoglycans to treat cardiac fibrosis in pathological remodeling, Circulation 137 (2018) 2497–2513.