The role of galectin-3 in cardiac remodeling and fibrogenesis
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Role of Galectin-3 Pathways in the Pathogenesis of Cardiac Remodeling and Heart Failure

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Abstract

Myocardial injuries stemming from pressure overload or myocardial infarction lead to cardiac remodeling and represent major health problems world-wide. An ever accumulating body of experimental and clinical research appoints galectin-3, a β-galactoside-binding lectin, as a key player in this maladaptive response to myocardial injury. Herein, a specific role for galectin-3 in inflammation and fibrogenesis has been elucidated in experimental and clinical studies. Galectin-3 was first associated with pathological conditions leading to cardiac remodeling, such as inflammation and fibrosis. Then, as the carbohydrate recognition domain of galectin-3 reacts with glycosylated proteins such as laminin, fibronectin and tenascin, a multifunctional role of galectin-3 in the extracellular matrix was postulated. Notably, experimental animal studies clearly showed that galectin-3 is a mediator of crucial steps in fibrogenesis, and further induces cardiac inflammation, hypertrophy and dysfunction. Possible mechanisms pertaining to galectin-3 inflammatory and fibrotic properties have been suggested to involve macrophage activation, galectin-3-induced chemotaxis and activation of the TGF-β-Smad3 signaling pathways. Additionally, the link between plasma galectin-3 and fibrosis was also established in clinical biomarker studies. Galectin-3 and its pathways may be explored further in order to develop more efficient strategies to target cardiac remodeling in heart failure leading to fibrosis.

**Key words:** Galectin-3 – heart failure – remodeling – biomarker
STRUCTURE, EXPRESSION AND FUNCTION OF GALECTIN-3

Galectin-3 is a 29-35 kDa chimaera-type galectin. Galectins form a large family of galactosidase binding lectins, but galectin-3 is the only member of the galectin family with an extended N-terminal domain (110-130 amino acids). This N-terminal domain is composed of tandem repeat sequences comprising nine amino acid residues and is connected to a C-terminal carbohydrate recognition domain (CRD) of about 130 amino acids [1, 2]. The CRD interacts with various glycosylated proteins, modulates cell-cell adhesion and cell signaling in the extracellular compartment [1]. Further, the galectin-3 CRD and collagen-like domains communicate with a variety of extracellular matrix proteins (ECM), carbohydrates (e.g., N-acetyllactosamine), and also unglycosylated proteins such as cell surface receptors (macrophage antigens CD11b/CD18) and extracellular receptors (collagen IV) [3-6], and they furthermore modulate cell-cell adhesion and cell signaling in the extracellular compartment.

Galectins are expressed in various cells and tissues and are important for diverse physiological and pathological processes, such as immune and inflammatory responses, tumor development and progression, neural degeneration, atherosclerosis, diabetes, as well as wound repair. Galectin-3 has been detected in many proliferative cells including tumor cells, eosinophils, neutrophils, and activated macrophages [7, 8]. Notably, many of these cells types are operative in the inflammatory response and the formation of fibrosis (fibrogenesis).

Galectin-3 is predominantly located in the cytoplasm. While intracellular galectin-3 plays a pivotal role in diverse cell growth, anti-apoptosis signaling, and mRNA splicing, extracellular (or cell surface bound) galectin-3, on the other hand, participates in cell-cell and cell-matrix adhesion, by binding to glycosylated ECM components, including laminin, fibronectin, tenascin, and Mac-2 binding protein [3, 4, 9-12]. Thus, extracellular galectin-3 appears in tight communication with factors involved in fibrogenesis.

Differential expression of galectin-3 has been reported for different murine organs. Herein, lower expression was found in cerebrum, heart, and pancreas, while moderate expression was found in liver, ileum, kidney and adrenal gland and high expression in lung, spleen, stomach, colon, uterus, and ovary [13]. Figure 1 displays an overview of galectin-3 distribution in various healthy tissues of different species – our data are in concert with results published by Kim and colleagues [13]. Notably, a growing body of evidence reveals that high expression levels of galectin-3 are closely associated with pathological conditions, specifically conditions pertaining to inflammation and fibrosis which are also key conditions in cardiac remodeling.

Localization of galectin-3 in damaged tissue

Inflammation and fibrosis are intertwined pathological states and galectin-3 has consistently been observed to be involved in these damage states.

Galectin-3 is not only secreted by activated macrophages but in situ hybridization and immunohistochemistry analysis showed that galectin-3 is highly distributed in the fibrotic
Figure 1: Immunohistochemical localization, protein and mRNA expression of galectin-3 in various tissues of different species. Galectin-3 immunoreactivity has been observed in heart (A), Lung (B), Liver (C), Spleen (D), and Kidney (E). F-I: Galectin-3 protein expression (assessed by Western blot) and mRNA expression (assessed by qPCR) has been predominantly observed in (mouse, rat, human) lung, testis/ovary, spleen, prostate, adipose tissue en skin. Picture A – E reprinted from reference [13] with permission from the publisher; Figure F – I: unpublished data (Yu et al.). Scale bars, 50 µm (A and B); 60 µm (C); 90µm (D); 400 µm(E).

area of myocardium and co-localizes to macrophages [14]. Moreover, an ever growing body of experimental evidence found that galectin-3 manifests in various damaged tissue, in particular in tissues with increased collagen deposition and localization in the fibrotic area [14-23]. Further, galectin-3 was expressed in proliferating fibroblast and was also found in nucleus when cells were exposed to apoptotic stimuli in vitro [24]. Moreover, galectin-3 expression has been detected in isolated cardiac fibroblast to localize galectin-3 binding sites. Interestingly, contrary to cardiac fibroblast, galectin-3 binding sites were absent from cardiomyocytes [7, 8, 14, 25-27].

GALECTIN-3 IN EXPERIMENTAL FIBROSIS

Early experimental support in liver, kidney and lung fibrosis
A prominent role for galectin-3 in fibrogenesis has been elucidated in recent years. Herein, work has specifically described fibrotic states in the liver, kidneys, pancreas and lungs. For example, galectin-3 showed to be temporarily and spatially associated with fibrosis with a minimal expression in healthy rat liver, while highest expression was found at peak fibrosis and virtually no galectin-3 expression was present after recovery from fibrosis [19]. Then, galectin-3 deficiency in bile duct ligated (BDL) rats was recently shown to significantly diminish BDL induced hepatic TGF-β1 and procollagen expression and associated hepatic fibrosis [28]. Additionally, in a murine model of cirrhosis, bone marrow cell transplantation significantly decreased liver fibrosis which was associated with decreased hepatic galectin-3 expression [29]. A recent report by Mackinnon et al [23] extended the involvement of galectin-3 to fibrosis in the lung. Authors found a significantly reduced TGF-β1 and bleomycin-induced lung fibrosis in galectin-3 deficient mice.

Likewise, galectin-3 expression and secretion by macrophages has been identified as a major contributor to renal fibrosis. Mice with galectin-3 deficiency did not show macrophage recruitment upon interferon-gamma/LPS stimulation [19]. Henderson et al. also observed that galectin-3 mediated TGF-β induced myofibroblast activation, a crucial step in the fibrogenesis cascade [17]. Lastly, the therapeutic potential of targeting galectin-3 to relieve fibrotic burden has recently been investigated by Kolatsi-Joannou and colleagues [30] who demonstrated that folic acid induced kidney fibrosis and associated galectin-3 expression was significantly reduced by 1% treatment with modified citrus pectin (MCP). MCP is a pectin derivative binding to the galectin-3 CRD thereby inhibiting galectin-3 aforementioned effects.

Altogether, a growing body of literature consistently supports a role of galectin-3 in fibrogenesis. This appears a generalized effect, not confined to one organ.

Fibrosis is also central to the maladaptive response to myocardial injury, such as pressure overload and myocardial infarction leading to cardiac remodeling [14, 21, 22] Supporting the notion that galectin-3 constitutes a global player in fibrogenesis, it is not surprising that galectin-3 has also been shown to be involved in myocardial fibrogenesis.

**Galectin-3 in cardiac remodeling pathway – recent experimental support**

The first evidence showing an involvement of galectin-3 in heart failure stems from a landmark study of Sharma and colleagues [14]. In a comprehensive microarray study galectin-3 was identified as the most robustly overexpressed gene in heart-failure prone hypertrophied hearts compared to functionally compensated hearts in homozygous transgenic TGFmRen2-27(Ren-2) rats. Ren-2 rats overexpress the mouse Ren-2d renin gene and spontaneously develop heart failure after 13-15 weeks. Further, continuous low-dose infusion of recombinant galectin-3 into the pericardial sac caused left ventricular dysfunction in healthy Sprague-Dawley rats, associated with collagen deposition and other signs of cardiac remodeling [14]. These initial observations warranted galectin-3 to be considered as a new target for intervention in heart failure.
Then, more recently, Sharma et al. [21] found a significant and high expression of galectin-3 in cardiac tissue of Ang-II induced hypertension in mice. In this model, galectin-3 was released by infiltrating macrophages in the myocardium and led to interstitial collagen deposition. Treatment with N-Acetyl-Ser-Asp-Lys-Pro (Ac-SDKP), an endogenous tetrapeptide specifically degraded by angiotensin converting enzyme (ACE), reduced macrophage activation and galectin-3 expression herein, and prevented galectin-3-induced cardiac inflammation, fibrosis and remodeling.

Additionally, Liu et al. showed that in galectin-3-induced cardiac remodeling, galectin-3 increased the number of macrophages, mast cell infiltration and activated the TGF-β/Smad3 pathway. Ac-SDKP partially or near completely prevented galectin-3 induced cardiac inflammation, fibrosis, hypertrophy and dysfunction, possibly by inhibition of the TGF-β/Smad3 signaling pathway [22].

Recent studies by Thandavaryan et al. [31], Kamal et al. [32] and by Psarras et al. [33] further reveal a specific association of galectin-3 with left ventricular dysfunction and fibrosis. Specifically, Thandavaryan et al. [31] found a significant increase in myocardial hypertrophy and fibrosis, as well as apoptosis, all associated with up-regulated galectin-3 in 14-3-3n protein mutant (DN-14-3-3n) mice after induction of diabetes. 14-3-3n protein has a regulatory role in apoptosis, adhesion, cellular proliferation, differentiation, survival and signal transduction pathways [34]. As the authors stated, up-regulated galectin-3 appears to be a general phenomenon in LV dysfunction [31]. Moreover, Kamal et al. [32] demonstrated that cardiac hypertrophy, progressive fibrotic cardiac remodeling with increased collagen deposition were accompanied with significantly increased galectin-3 expression in cardiomyopathic hearts in a rat model of myosin-induced experimental autoimmune myocarditis (EAM). Notably, herein galectin-3 over-expression was dramatically reduced by treatment with T-3999, a novel phenylpyridazinone, indicating an inhibitory function of T-3999 on galectin-3.

Then, Psarras et al. [33] found that desmin deficient (des/-/-) mice exhibit marked myocardial degeneration and fibrosis, which were associated with osteopontin (OPN) and galectin-3 overexpression (226x for OPN and 26x for galectin-3). OPN, like galectin-3, has chemotactic properties and is thus recruited to inflammatory sites [35, 36]. Psarras et al. [33] further compared des/-/- OPN -/- mice with des/-/- OPN +/- mice and found that des/-/- OPN -/- mice not only displayed remarkable improvements in ventricular function (53%) but also in myocardial fibrosis (44%) while also significantly reducing galectin-3 gene expression (by ≈80%) compared to des/-/- OPN +/- mice, indicating that the observed diminished inflammatory and fibrotic response in OPN deficient des/-/- mice could be partly explained by the significant reduced myocardial galectin-3 level [33].

So, accumulating experimental evidence implicates a role of galectin-3 in the development of organ fibrosis. Whether galectin-3 is a potential therapeutic target in left ventricular (LV) remodeling and heart failure is unknown. We have conducted experimental studies and our results suggest galectin-3 may a target for therapy. Genetic disruption and
pharmacological inhibition of galectin-3 attenuated adverse LV remodeling, fibrosis and subsequent HF development. We perturbed mice with angiotensin II (AngII) and transverse aortic constriction (TAC) causing LV hypertrophy, decreased LV contractility and increased LV end-diastolic pressure, associated with increased fibrosis in wild type (WT) mice. However, galectin-3 knock out (Gal3-KO) mice did not develop LV dysfunction and fibrosis. Additionally, in homozygous TGR(mREN)27 rats, pharmacological inhibition of galectin-3 with an oligosaccharide almost completely prevented LV dysfunction and fibrosis [54, 55].

This indeed suggests that drugs binding to galectin-3 may be potential therapeutic candidates for the prevention of heart failure with extensive fibrosis. It remains unclear what mechanisms underpin these effects.

**ROLE OF GALECTIN-3 IN MODULATION OF FIBROSIS**

### Potential mechanism of galectin-3 in extracellular matrix

Fibroblasts, myofibroblasts and macrophages have been identified as important cells in the initiation and progression of fibrogenesis, scar formation, and tissue remodeling [37-39]. Extracellular matrix remodeling (ECM) is a crucial aspect in fibrogenesis and galectin-3 seems to play a multifunctional role in the ECM environment, as its CRD reacts with glycosylated proteins in the ECM, such as laminin, fibronectin, tenascin [3, 4], as well as membrane proteins, such as αM/β2 (CD11b/18) [40].

### Potential mechanisms of galectin-3 in myofibroblast differentiation

Fibroblast to myofibroblast differentiation and activation by inflammatory cytokines, like TGF-β, preceded by influx of cells such as macrophages are some of the initial steps in the process of fibrogenesis. A large body of research supports a role for galectin-3 in this process. Herein, it appears that macrophages and TGF-β induce myofibroblast activation via galectin-3, but that macrophage recruitment and TGF-β expression is independent of galectin-3.

First, galectin-3 was visualized in the fibrotic area co-localizing with fibroblasts and macrophages [14]. Second, it was shown that infusion of recombinant galectin-3 into pericardial sac leads to inflammatory cell infiltration, cardiac fibroblast proliferation, collagen synthesis and deposition, essentially contributing to interstitial and perivascular fibrosis [14, 21, 22]. Then, Dvorankova et al. demonstrated myofibroblast activation *in vitro* upon treatment with a moderately high dose recombinant galectin-3 [41]. Further, galectin-3 deficiency significantly reduced myofibroblast activation in carbon tetrachloride (CCL4) induced hepatic fibrosis and renal fibrosis (in a model of unilateral ureter obstruction, UUO) [17, 19].

Then, macrophages regulate fibroblast and myofibroblast activation in ECM and macrophage derived galectin-3 presents in various fibrotic pathologies. Injured tissue displays a marked increase in galectin-3 expression by activated macrophages and also an increased TGF-β expression, all these factors promote fibroblast proliferation and myofibroblast activation [17]. Macrophage depletion, then, significantly inhibits myofibroblast activation.
and decreases fibrosis [19]. For example, Henderson and colleagues showed that galectin-3 deficient macrophage recruitment could not drive myofibroblast accumulation and activation. Utilizing a cross-over experiment with wild-type or galectin-3 deficient macrophage supernatant and galectin-3 deficient renal fibroblast, these authors further observed that proliferation of galectin-3 deficient renal fibroblasts were activated by wild-type macrophages and attenuated by a galectin-3 inhibitor bis-(3-deoxy-3-{3-methoxybenzamido}-β-D-galactopyranosyl-sulfane), while galectin-3 deficient macrophages did not induce proliferation in galectin-3 deficient renal fibroblasts.

On the other hand, galectin-3 deficiency markedly reduces activated myofibroblast but does not affect macrophage recruitment nor pro-inflammatory cytokine profiles in injured tissue, such as IL-6 and TNF-α. Additionally, while galectin-3 deficiency led to reduced collagen deposition and reduced myofibroblast activation, TGF-β expression or smad2/3 phosphorylation were not influenced [19].

Furthermore, our unpublished galectin-3 chemotaxis assay results show that recombinant galectin-3 significantly induces monocyte migration, which could be markedly attenuated after treatment with galectin-3 inhibitors including modified citrus pectin (MCP) and lactose. These inhibitors act as a ligand, binding to galectin-3’s CRD.

Altogether, these events clearly indicate galectin-3 to be a key player in the signal axis of fibrosis generation, specifically inducing macrophage and TGF-β induced myofibroblast activation [17, 19, 23, 42].

**CLINICAL UTILITY OF GALECTIN-3**

Clinical trials have consistently indicated a potential clinical utility of galectin-3 as a biomarker for prognosticating heart failure. Herein, van Kimmenade et al. were the first to evaluate the prognostic and predictive value of galectin-3 as a biomarker in acute heart failure [43], in the Pro-BNP investigation of dyspnea in the emergency department (PRIDE). While N-terminal pro brain natriuretic peptide (NT-proBNP) was a superior predictor for diagnosis of acute heart failure compared to galectin-3 and apelin (herein galectin-3 was a better predictor than apelin) Figure 2A, galectin-3 was the superior predictor compared to NT-proBNP and apelin for prognosis in acute heart failure. Multivariate logistic regression analysis revealed that elevated plasma levels of galectin-3 were indeed the most powerful predictor for death, or the combination of death and recurrent heart failure within 60 days.

Plasma galectin-3 levels were related to detailed echocardiographic examinations in substudy (N =115) of the PRIDE [44]. Galectin-3 levels were not strongly related to markers of LV structure or systolic function, but related to measures of RV function and diastolic dysfunction, and highest galectin-3 concentrations were strongly associated with a higher risk of 4 year mortality, is independent from LV dimensions, function, and RV pressure, supporting the role galectin-3 may play in fibrosis and progressive cardiac failure.
Figure 2 Galectin-3 as a biomarker; data from several clinical trials.

**Figure 2A:** Combined receiver-operating characteristic (ROC) curves for amino-terminal pro-brain natriuretic peptide (NT-proBNP), galectin-3 and apelin for the diagnosis of heart failure in dyspneic patients. The ROC analysis for NT-proBNP showed an area under the curve (AUC) for NT-proBNP of 0.94 (p = 0.0001). The ROC analysis for galectin-3 showed an AUC of 0.72 (p = 0.0001). The AUC for apelin for diagnosis of acute heart failure was 0.52 (p = 0.23). This figure was reprinted from van Kimmenade et al. [43], with permission.

**Figure 2B:** Mortality as a function of baseline galectin-3 and NT-proBNP categories. The median value of NT-proBNP (253 pmol/L), was used to define two levels of NT-proBNP concentration. Of the 232 subjects, 231 had both a galectin-3 and NT-proBNP measurement. The number of patients in each category is as follows: high galectin-3 and high NT-proBNP (n=66); low galectin-3 and low NT-proBNP (n=69); low galectin-3 and high NT-proBNP (n=49); high galectin-3 and low NT-proBNP (n=47). Reprinted from reference [46] by Lok et al., with permission.

**Figure 2C:** Graphical depiction of the risk estimates for experiencing the primary outcome in patients with HFPEF and HFREF with increasing levels of plasma galectin-3. The distribution of (log-transformed) galectin-3 is depicted in the background in brown bars. A similar increase in galectin-3 causes a much more pronounced increase in risk in patients with HFPEF compared to patients with HFREF. Figure reprinted from reference [47] by de Boer et al, with permission.

**Figure 2D:** Graph showing galectin-3 levels in male (blue line) and female subjects (red line) from the general population. Grey-shaded areas indicate 95% confidence intervals. Galectin-3 levels increase with increasing age, particularly in female subjects. This figure is reprinted from reference [49] by de Boer et al., with permission.
Further and specifically relating galectin-3 to fibrosis, plasma galectin-3 levels were significantly correlated with several serum markers of cardiac ECM turnover, such as PIIINP, MMP-2 and TIMP-1, in 106 patients with chronic heart failure (New York Heart Association class II-III; mean LV ejection fraction [LVEF], 35±9%) [45]. Subsequently, Milting et al. described the kinetics of galectin-3 in 55 end stage heart failure patients with the need for mechanical circulatory support (MCS). Notably, this study found that fibrosis related biomarkers, such as tissue inhibitor of metalloproteinase (TIMP), tenascin C (TNC), OPN, BNP and galectin-3 were all increased in patients with terminal heart failure. Interestingly, MCS only reduced the loading related biomarker BNP, but none of the other fibrosis related biomarkers. Additionally, patients who did not survive on MCS had higher baseline galectin-3 levels when compared with patients who lived until transplantation [45].

Then, a larger study by Lok et al. comprising 232 patients with chronic heart failure (New York Heart Association function class III or IV) demonstrated that patients with high baseline levels of both galectin-3 and NT-proBNP had around 1.5- to 2-fold higher mortality rate Figure 2B [46]. This study demonstrated incremental value of galectin-3 over NT-proBNP alone.

Additionally, a large study of 592 patients with heart failure (Coordinating study evaluating outcomes of Advising and Counseling in Heart failure, COACH trial, [47]), with mean follow-up of 18 months supported prognostic value of galectin-3 to predict re-hospitalization and death after correction for age, gender, BNP, eGFR and diabetes, but not after correction for LVEF. A subanalysis revealed that increased plasma galectin-3 levels represents a stronger incremental risk in patients with preserved LVEF (HFPEF) compared to the patients with reduced LVEF (HFREF) (P<0.001) even when absolute galectin-3 levels did not differ between patients with HFPEF and HFREF [47] Figure 2C.

Furthermore, in the HF-ACTION study where plasma galectin-3 levels were assessed in 895 subjects with heart failure from a randomized, controlled trial of exercise training in patients with chronic heart failure with NYHA class II, III or IV symptoms, galectin-3 was associated with NYHA class, lower systolic blood pressure, higher creatinine, higher NT-proBNP, and lower maximal oxygen consumption. However, this association diminished after adjustment for NT-proBNP [48].

Finally, recent data show that small increases in galectin-3 may confer increased CV risk in the general population, in subjects at risk for heart failure development. Briefly, 7968 subjects were included in this study from the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort (mean age of 50 ± 13 years, median follow-up of approximately 10 years). Plasma galectin-3 levels correlated very strong with age and sex Figure 2D, and weakly with a wide range of risk factors of CV disease, including blood pressure, serum lipids, body mass index, renal function and NT-proBNP. After correction for classical CV risk factors (smoking, blood pressure, cholesterol and diabetes), increased plasma galectin-3 levels independently predicted all-cause mortality in a large community-based cohort [49].
Altogether, these available clinical studies have so far confirmed that plasma galectin-3 levels was significantly up regulated in acutely decompensated heart failure\cite{43, 44, 50, 51}, chronic heart failure \cite{46-49} and end-stage heart failure with the need for mechanical circulatory support (MCS) \cite{52}. Furthermore, clinical results from our group further demonstrated the predictive and prognostic value of galectin-3 \cite{46, 47, 49}. A relationship between galectin-3 and cardiovascular (CV) risk factors was investigated in the general population of PREVEND study, and a strong gender specific interaction was revealed in the correlation between galectin-3 and cardiovascular risk factors \cite{49}. Notably, the established link between plasma galectin-3 and fibrosis was also established in clinical biomarker studies \cite{52} and needs to be explored further in order to develop more efficient strategies to target cardiac remodeling in heart failure leading to fibrosis.

**CONCLUSION AND MAPPING OF GALECTIN-3 PATHWAYS**

In conclusion, galectin-3 is highly expressed in the fibrotic area of the failing or stressed heart \cite{14, 17, 19, 21, 22} and cardiac fibroblasts and macrophages are the main sources of galectin-3. Further, galectin-3 was shown to activate the TGF-β/Smad3 pathway \cite{22}, while

**Figure 4:** Working scheme representing the sequence of events following an index event (such as myocardial infarction (MI), hypertension, myocarditis and cardiomyopathy) leading to remodeling and non-remodeling heart failure. The graph within this graphic is taken from de Boer et al. \cite{8} and represents the adjusted Cox regression curves for quartiles of plasma galectin-3 showing the cumulative risk for the combined end-point, death. The back circles with the white numbers represent quartile 1 through 4, respectively. Galectin-3 is displayed as a central modulating factor involved in the remodeling process which leads to ongoing damage and eventually poor heart failure outcome. Therapeutically, galectin-3 inhibition could favor non-remodeling heart failure, thereby potentially improving heart failure outcome. Figure reprinted from reference \cite{56} by de Boer et al. with permission.
macrophages and the inflammatory factor TGF-β demonstrated to elevate galectin-3 expression. Then, galectin-3 inhibition or deficiency was found to not affect macrophage activation and TGF-β expression levels. Therefore, galectin-3 may be considered as an independent participant in macrophage and TGF-β/Smad modulation pathway.

Other experimental animal studies reported that galectin-3 was not only significantly associated with myofibroblast induced collagen synthesis and deposition but was also markedly correlated with ECM fibrosis markers, such as: α-SMA, COL1A1, COL3A1, TIMP, MMP [53] Figure 3(see Chapter 2 Figure 1).

Lastly, relevant clinical studies identified that plasma galectin-3 is significantly correlated with serum extracellular fibrosis turn over biomarkers, like PINP, PIIINP, TIMP, MMP. Collectively, galectin-3 may be suggested as “culprit biomarker” involved in pathophysiology circle of cardiac remodeling and heart failure. A suggested pathway of galectin-3 is displayed in Figure 4 [56].

Data from experimental renal damage and cancer suggest to galectin-3 is a feasible target for therapy. Our pilot data lend support to the notion that also in heart failure galectin-3 may be a target for therapy. More research is warranted herein, specifically, at what stage galectin-3 comes into play and what the ideal window would be for intervention. Most data show that preventative regimen might work, but if fibrosis, once ensued, could be attenuated or reversed is also unknown. From a clinical point of view this is of utmost importance.

Disclosures

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References


