# Galectin-3 in Cardiac Remodeling and Heart Failure

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**Abstract** Galectin-3 is a member of the galectin family, which consists of animal lectins that bind β-galactosides. Recently, a role for galectin-3 in the pathophysiology of heart failure has been suggested. It was observed that galectin-3 is specifically upregulated in decompensated heart failure compared with compensated heart failure in animal models of heart failure. This has been associated with activation of fibroblasts and macrophages, which are a hallmark of cardiac remodeling. Therefore, galectin-3 may be a culprit biomarker in heart failure. Initial clinical observations indicate that galectin-3 may be a useful biomarker for decompensated heart failure, with incremental value over well-used "pressure-dependent" biomarkers, such as B-type natriuretic peptide. Future studies should focus on galectin-3 biology to better address the usefulness of galectin-3 as a biomarker and probe the usefulness of anti-galectin-3 therapy in treating heart failure.

**Keywords** Galectin 3 · Heart failure · Prognosis · Fibrosis · Macrophages · Biomarkers · Renin-angiotensin system

## Introduction

Galectins are a family of lectins that bind β-galactosides [1, 2]. Galectins are expressed in vertebrates such as fish, birds, amphibians, and mammals, but also in invertebrates (worms, insects) and even in lower organisms such as sponge and fungus [1, 2], which suggest an important role in biology. Currently, 15 members of the galectin family have been described in vertebrates.

All galectins bind carbohydrate via carbohydrate-recognition domains (CRDs), with many conserved sequence elements that are typically about 130 amino acids. Some galectins contain just one CRD (galectins 1, 2, 5, 7, 10, 11, 13, 14, and 15), others (tandem repeat-like) galectins contain two homologous CRDs in a single polypeptide chain, separated by a linker of up to 70 amino acids (galectins 4, 6, 8, 9, and 12), whereas galectin-3 contains a nonlectin N-terminal region (about 120 amino acids) connected to a CRD, often referred to as a chimera-like galectin. Each galectin has an individual carbohydrate-binding preference. Most galectins are bivalent or multivalent with regard to their carbohydrate-binding features: one-CRD galectins may form dimers; two-CRD galectins have two carbohydrate-binding sites; whereas galectin-3 forms pentamers upon binding to multivalent carbohydrates. Therefore, galectins can form ordered "arrays" made of lectin and multivalent glycoconjugates [3, 4••].

Galectins are primarily localized in the cytoplasm, but can also be localized in the nucleus. Although galectins can be secreted, they do so without a specific signal sequence. Galectin family members do not contain a classical signal sequence. Consistent with this feature, the proteins are localized primarily in the cytoplasm, although also in the nucleus under certain conditions. However, they can be secreted and thus belong to the group of proteins that do not contain a signal sequence but can function outside cells [5].

Galectins may bind to different cell surface antigens and receptors in a carbohydrate-dependent manner. It has been suggested that galectins may not have specific individual receptors, but that each galectin can bind to a set of cell surface or extracellular matrix glycoproteins containing suitable oligosaccharides. Recent studies have demonstrat-

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ed that galectins also exert intracellular functions, such as signal transduction, by binding to intracellular ligands and participating in intracellular signaling pathways [6].

## Galectin-3: Biology and Expression

### Biology

Galectin-3 (sometimes also referred to as Mac-2, carbohydrate-binding protein [CBP]-35, εBP, RL-29, HL-29, L-34, or lipopolysaccharide-binding protein [LBP]; size: 31KDa) is found in solution as a monomer with two functional domains [7–9]. Galectin-3 is unique for having an extra N-terminal domain of about 100 to 150 amino acids long, rich in proline, glycine, tyrosine, and glutamine [10]. Galectin-3 has high affinity for lactose and N-acetyllactosamine; affinity for N-acetyllactosamine is about fivefold higher than for lactose; ligands containing poly-N-acetyllactosamine sequences use galectin-3 as a receptor. Galectin-3 is a unique chimera-like galectin. This means that galectin-3 consists of carbohydrate recognition and collagen-like domains, which makes it able to interact with a wide array of extracellular matrix proteins, carbohydrates (eg, N-acetyllactosamine), and unglycosylated molecules, such as cell surface receptors (macrophage CD11b/CD18) and extracellular receptors (collagen IV). Galectin-3 mainly binds to glycosylated proteins of the matrix, including laminin, fibronectin, and tenascin [11, 12]. This has extensively been reviewed by Krzéslak et al. [10] and Ochieng et al. [13] (Table 1).

Galectin-3 is localized in the cytoplasma and the nucleus. Loss of nuclear galectin-3 is believed to affect the malignant phenotype of cancers. Nuclear expression of galectin-3 is associated with proliferative effects and it has been described that galectin-3 translocates from the cytosol into the nucleus via a passive and an active pathway [14]. Galectin-3 contains several phosphorylation sites and other determinants important for the secretion of galectin-3, which proceeds via a novel, nonclassical pathway [15]. Through its interaction with extracellular matrix proteins, galectin-3 can cross the plasma membrane despite its lack of appropriate signal peptides. Secretion of galectin-3 is critically regulated at the plasma membrane [16].

### Expression of Galectin-3

The different members of the galectin family exhibit a specific pattern of expression in various cells and tissues. Expression of galectin-3 has been detected in macrophages, eosinophils, neutrophils, and mast cells [17, 18]. In tissues, galectin-3 is most abundantly expressed in lung, spleen, stomach, colon, adrenal gland, uterus, and ovary [19].

Galectin-3 is also expressed, albeit at a much lower level, in kidney, heart, cerebrum, pancreas, and liver [19]. However, under pathophysiologic conditions, the level of expression of galectin-3 may change substantially so that a low constitutive expression level of galectin-3 does not preclude a prominent function (eg, in liver and heart).

## Galectin-3 in Cardiac Remodeling and Heart Failure

### Experimental Observations

The observation that galectin-3 is increased in decompensated heart failure has been published in a seminal paper by Sharma et al. [20]. The authors studied homozygous Ren-2 rats that overexpress the murine *Ren-2d* renin gene, resulting in severe hypertension with end-organ damage [21, 22]. It was observed that, although some rats experience overt failure after about 15 weeks, with signs of heart failure such as dyspnea, lethargy, and severely compromised hemodynamics, some rats remain compensated. These two groups were compared using a complementary DNA array with whole RNA from rat hearts. It was observed that a set of 48 genes were differentially regulated [20, 23]. Interestingly, most differentially regulated genes typically encoded matricellular proteins, such as collagens, osteoactivin, and fibronectin, but not loading-dependent factors, such as natriuretic peptides [23]. Galectin-3 was the strongest regulated gene, being up-expressed in decompensated hearts more than fivefold compared with compensated hearts.

To dissect cause from consequence, Sharma et al. [20] showed that infusion with galectin-3 in the pericardial sac of normal rats led to the development of cardiac remodeling with dysfunction and increased expression of collagens. Given the upregulation of galectin-3 well before the transition to overt heart failure, the authors concluded that galectin-3 may be a factor that should be considered as a novel target for intervention in heart failure.

Thandavarayan et al. [24] recently described a model with cardiospecific expression of a dominant-negative form of 14-3-3 protein, which regulates apoptosis and several signaling pathways that leads to left ventricular (LV) dysfunction. Besides typical changes for LV remodeling, such as hypertrophy, fibrosis, and apoptosis, the authors also describe an upregulation of galectin-3 in the LV [24]. Therefore, upregulation of galectin-3 may be a general phenomenon in LV dysfunction and not be confined to models with increased angiotensin II (AngII) signaling.

A potential role in mediating the effects of galectin-3 has been suggested for N-acetyl-Ser-Asp-Lys-Pro (ac-SDKP), a tetrapeptide degraded by angiotensin-converting enzyme (ACE) [25, 26•]. First, researchers showed that differenti-

**Table 1** Ligands for galectin-3

|  | Ligand | Source /cells |
|---|---|---|
| Extracellular matrix proteins | Laminin | EHS, macrophage, placenta |
|  | Fibronectin | Foetal |
|  | Tenascin | Brain |
|  | M2BP | Brain |
| Membrane proteins | Integrins | Macrophage |
|  | αM/β2 (CD11b/18) | Adenocarcinoma |
|  | α1/β1 | Mouse brain |
|  | NCAM | Mouse brain |
|  | L1 | Mouse brain |
|  | MAG | Ubiquitous |
|  | LAMP-1/LAMP-2 | Rat lens |
|  | MP20 | Human T lymphoma |
|  | CD98 | Jurkat cells |
| Intracellular proteins | Cytokeratins | HeLa, MCF-7 |
|  | Chrp | Murine T3 fibroblasts |
|  | CBP70 | HL60 |
|  | Alix/AIP-1 | Human T Lymphoma |
|  | Bcl-2 | Jurkat cells |
|  | Gemin-4 | Human T lymphoma |
|  |  | Jurkat cells |
|  |  | HeLa |
| Others | AGE | Ubiquitous |

*AGE* advanced glycation end products; *CBP70* glucose-binding protein; *EHS* Engelbroth-Holm-Swarm tumor laminin; *LAMP* lysosomal-associated membrane protein 1; *M2BP* Mac-2 binding protein; *MAG* myelin-associated glycoprotein; *MP20* membrane protein 20; *NCAM* neural cell adhesion molecule

(*From* Krzeslak et al. [10])

ation of murine bone marrow cells to macrophages was inhibited by ac-SDKP. Second, in mice treated with angiotensin II, ac-SDKP reduced fibrosis and expression of galectin-3 in LV tissue [25]. In a second study, LV remodeling was induced by infusion of galectin-3 in the pericardial sac [26•], with or without coadministration of ac-SDKP. As in the initial report by Sharma et al. [20], galectin-3 enhanced macrophage and mast cell infiltration, which is associated with development of interstitial and perivascular fibrosis and LV dysfunction. Ac-SDKP prevented these events, in whole or in part, and these effects were shown to be mediated by transforming growth factor (TGF-β)/Smad3 pathway.

## Fibrosis

Galectin-3 seems to be particularly involved in fibrosis. Fibrosis and scar formation are pivotal processes in maladaptive cardiac remodeling. Fibroblasts, myofibroblasts, and macrophages have been identified as important cells in the initiation and progression of tissue scarring [27–29]. Various fibrotic conditions are associated with upregulation of galectin-3: liver cirrhosis [30, 31], idiopathic lung fibrosis [32], and chronic pancreatitis [33]. In animal models, upregulation of galectin-3 has been described for hepatic [31], renal [34, 35•, 36], and cardiac [20, 25, 26•] fibrosis.

More detailed study into the role of galectin-3 in cardiac remodeling revealed that galectin-3 was localized at the very sites of fibrosis, colocalizing with fibroblasts and macrophages, but not with cardiomyocytes. Galectin-3 binding sites were visualized by biotinylated antibodies and localized predominantly to fibrotic areas [20], in line with the evidence that galectin-3 binds extracellular proteins. Furthermore, recombinant galectin-3 causes proliferation and collagen production of cardiac fibroblast cultures in vitro. Other published data corroborate these observations [25, 26•].

Galectin-3 has also been identified as a potentially important mediator of removal of advanced glycosylation end-products (AGEs) [37]. AGEs are molecules formed during a nonenzymatic reaction between proteins and sugar residues. They accumulate in the human body with age, but also with enhanced states of oxidative stress, increased intake of AGEs, and renal and heart failure, and are thought to contribute to myocardial stiffening [38]. An AGE-specific cellular receptor complex (AGE-R) mediating AGE removal has been described. Galectin-3 interacts with AGE-R components, thus contributing to the elimination of these pathogenic substances. Galectin-3 disruption is associated with increased susceptibility to AGE-induced renal disease, which indicates that galectin-3 is operating in vivo as an AGE receptor to afford protection toward AGE-dependent tissue injury [39, 40]. It remains unknown whether galectin-3 acts on AGE biology in the heart.

Other experimental lines of evidence provide further compelling evidence that galectin-3 is a key player in fibrosis. Especially the generation of galectin-3 deficient mice has been instrumental in the study of galectin-3 in fibrosis. Henderson et al. [31, 35•] has published papers on the role of galectin-3 in hepatic and renal fibrosis. In the liver, TGF-β via galectin-3 activates myofibroblasts. In the kidney, galectin-3 expression and secretion by macrophages is a major mechanism in renal fibrosis.

## Inflammation

Besides fibrosis, galectin-3 plays an important role in the inflammatory response, which is an important player in the process of cardiac remodeling [41]. In renal models of inflammation, galectin-3 has been convincingly linked to fibrosis and damage [34, 36]. Employing a model of murine renal fibrosis, Henderson et al. [35•] established that depletion of macrophages significantly reduced myofibroblast activation and decreased fibrosis. In the heart, no direct evidence has been generated for inflammatory effects via galectin-3, although Sharma et al. [20] noted that, besides galectin-3, other genes encoding for immune factors were differentially regulated. Mice that constitutively express interferon-γ in their livers develop myocarditis, with macrophages expressing high levels of galectin-3 [42].

## Clinical Studies

Sharma et al. [20] provided the first report in human subjects. They studied ventricular biopsies from patients with aortic stenosis with preserved or depressed ejection fraction and showed that galectin-3 was upregulated in the biopsies from patients with depressed ejection fraction. van Kimmenade et al. [43] published the first clinical study that evaluated the potential role of galectin-3 as a plasma biomarker in heart failure. In this study, 599 acutely dyspneic subjects were evaluated with the goal to establish the usefulness of N-terminal prohormone brain natriuretic peptide (NT-proBNP), galectin-3, and apelin in diagnosing heart failure and predicting outcome. A blood sample was collected at baseline, and NT-proBNP, galectin-3, and apelin were measured later. A total of 209 patients were diagnosed with heart failure. NT-proBNP was the most powerful predictor for diagnosing heart failure. Receiver operating characteristic analysis examining the value of NT-proBNP for the diagnosis acute heart failure showed an area under the curve (AUC) for NT-proBNP of 0.94 ($P<0.0001$), whereas the AUC for galectin-3 for the diagnosis acute heart failure was 0.72 ($P < 0.0001$). The difference between NT-proBNP and galectin-3 being highly

Fig. 1 Galectin-3 pathways. The network represents molecular relationships among different gene products. Node shapes indicate the functional class of the gene product, whereas node colors indicate a role in general fibrosis (*orange*) or cardiac fibrosis (*green*). Edge colors indicate upregulation or activation (*red*), downregulation or inhibition (*green*), or involvement without clear directionality (*yellow*). All relationships are supported by references from the Ingenuity Pathway Knowledge Base or key reference included in the review by de Boer et al. [47•]. *ACE* angiotensin-converting enzyme; *Ac-SDKP* N-acetyl-Ser-Asp-Lys-Pro; *AKT1* RAC-α serine/threonine-protein kinase; *CCND1* cyclin D1; *CDKN1A* cyclin-dependent kinase inhibitor 1A; *COL1A1* collagen, type I, α-1; *COL4A1* collagen α-1(IV); *ERK* extracellular signal-regulated kinase; *FN1* fibronectin; *IL1RL1* interleukin 1 receptor-like 1; *IL33* interleukin 33; *INHBA* inhibin β A; *MMP* matrix metalloproteinase; *MYC* v-myc myelocytomatosis viral oncogene homolog (avian); *NADPH* nicotinamide adenine dinucleotide phosphate; *PI3K* phosphoinositide 3-kinase; *PTEN* phosphatase and tensin homolog; *PTK2* protein tyrosine kinase 2; *TGFB1* transforming growth factor β-1; *TIMP* tissue inhibitor of metalloproteinases; *TMSB4X* thymosin β-4; *TNF* tumor necrosis factor; *TP53* tumor protein p53; *RELA* V-rel reticuloendotheliosis viral oncogene homolog A, nuclear factor of κ light polypeptide gene enhancer in B-cells 3, p65 (avian). (*From* de Boer et al. [47•], with permission.)

significant ($P < 0.0001$). The optimal cut-off of galectin-3 in this study was 6.88 ng/mL, which resulted in a reasonable sensitivity of 80% but a poor specificity of 52% [43]. For predicting short-term prognosis (60 days, primary end-point rehospitalization caused by heart failure [$n=60$] or all-cause mortality [$n = 17$]), galectin-3 was the most powerful predictor: an AUC for galectin-3 of 0.74 ($P=0.0001$) and an AUC for NT-proBNP of 0.67 ($P = 0.009$), with the difference being borderline significant ($P = 0.05$). In multivariate analysis, galectin-3 was the strongest predictor for death and the combination of death and rehospitalizations for heart failure. Remarkably, well-known predictors for outcome, such as NT-proBNP and renal function, were not predictive in this study. Nevertheless, this study provides strong support for the exploration of galectin-3 as a biomarker that may predict prognosis, whereas its usefulness in detecting heart failure or adding incremental value (over currently used clinical correlates and NT-proBNP) in the diagnostic work-up of heart failure remains unclear.

In a larger study in patients with chronic heart failure ($n = 232$), showed that galectin-3 predicts long-term outcome (mean follow-up, 3.4 y; HR, 1.95; 95% CI, 1.24–3.09; $P=0.004$; unpublished data, Lok et al.). Because not many other biomarkers of heart failure were measured, it is impossible to value the precise role of galectin-3 in this cohort from this study.

An interesting mechanistic study by Milting et al. [44] describes the kinetics of galectin-3 in 55 patients with end-stage heart failure with the need for mechanical circulatory support (MCS). This small study determined several biomarkers especially related to myocardial fibrosis and remodeling. First, the fibrosis-related biomarkers including
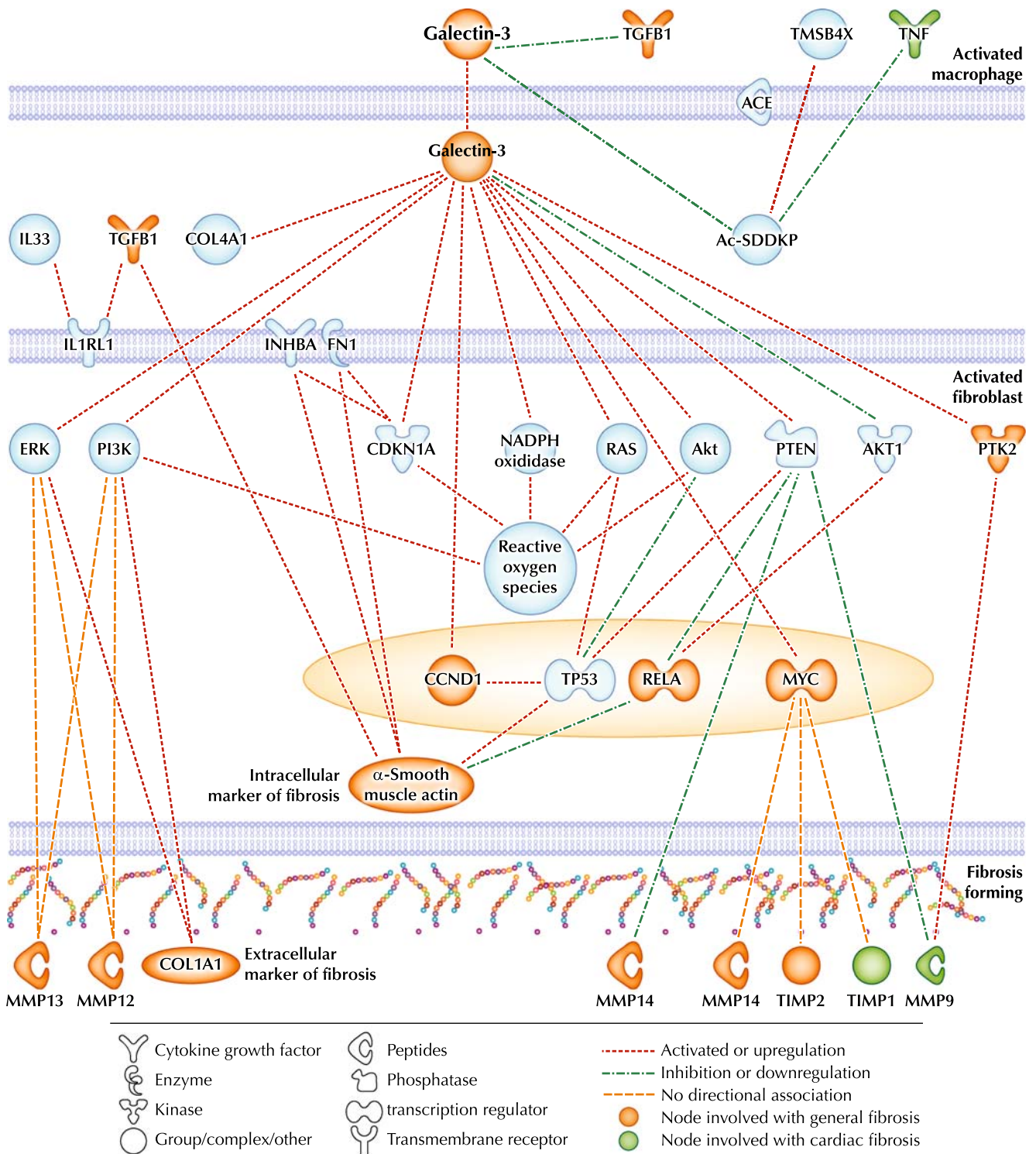
galectin-3 were increased compared with controls. Second, the authors reported that no fibrosis-related biomarkers, such as tissue inhibitor of metalloproteinases-1 (TIMP-1), tenascin, osteopontin, or galectin-3, were reduced by MCS; only the loading-related biomarker BNP was reduced by MCS. Third, patients who did not survive on MCS,

compared with patients who lived until transplantation, had higher baseline galectin-3 levels.

A recent study by Lin et al. [45] described the relation between serum galectin-3 and markers of extracellular matrix turnover. They studied 106 patients with chronic heart failure (New York Heart Association class II-III; mean

LV ejection fraction [LVEF], 35±9%). Serum aminoterminal propeptide of procollagen type I (PINP) and type III (PIIINP), matrix metalloproteinase-2 (MMP-2), and TIMP-1 were analyzed, along with galectin-3. Galectin-3 was correlated with PIIINP, TIMP-1, MMP-2, but not with LVEF, age, and sex. After correction, the correlation between galectin-3 and PIIINP and MMP-2 remained statistically significant. The authors conclude that these findings suggest a relationship between gelactin-3 and extracellular matrix turnover.

Taken together, from available clinical data, plasma and/ or serum galectin-3 is increased in acute and chronic heart failure. It seems that galectin-3 may be of particular value to predict prognosis. However, for clinical diagnosing and/or decision making, it seems less powerful, although we do not have sufficient data available.

## Conclusions

Galectin-3 is an interesting and complex protein with many effects in many organs. In the failing or stressed heart, it has been shown that activated macrophages secrete galectin-3. The increased expression levels of galectin-3 are associated with the tendency to develop decompensated heart failure, and in clinical cohorts, increased plasma galectin-3 levels are linked with worse prognosis. Therefore, galectin-3 may be advocated as a novel biomarker, but it may also be in the pathophysiologic circle of heart failure ("culprit biomarker"), and therefore it may also be a target for intervention [46•]. The suggested pathways of galectin-3 are displayed in Fig. 1 [46•].

There are several fields of uncertainty. First, we do not know how galectin-3 is regulated at a transcriptional and translational level in the heart. Mechanistic studies have provided evidence that cardiac fibroblasts and macrophages are the main sources for galectin-3, and that the TGF-β/Smad pathway is involved. Inflammatory signals also contribute in the regulation of galectin-3. However, it remains largely enigmatic which signals govern the production and secretion of galectin-3. Second, although several lines of evidence strongly suggest a contributory role for galectin-3 in the pathophysiology of heart failure, we lack proof-of-principle experiments (eg, in galectin-3 deficient mice or in pharmacologic studies) to show that galectin-3 is unequivocally contributing to the onset and progression of cardiac remodeling. Finally, we have no data if therapy, or which therapy, may affect galectin-3 expression and signaling.

Taken together from available clinical data, plasma and/or serum galectin-3 is increased in acute and chronic heart failure. It seems that galectin-3 may be of particular value to predict prognosis in heart failure; the cause for clinical diagnosing and/or decision making is less convincing; and to date we do not have data available to support the use of

galectin-3 for this purpose. Parallel to experiments described by Sharma et al. [20], we have observed that galectin-3 is upregulated in compensated and decompensated hypertrophy compared with healthy control rats; however, the difference is lesser than when comparing decompensated versus compensated rats (de Boer, unpublished data). This suggests that galectin-3 may be of lesser importance during the early stages of the disease. Furthermore, no data on serial measurements of galectin-3 have been published. Therefore, we lack data on half life, kinetics, clearance, and other parameters of galectin-3 biology. Milting et al. [44] suggest that acute unloading by MCS only reduces typical "loading" biomarkers (ie, BNP [or NT-proBNP]), not so much biomarkers associated with turnover of the extracellular matrix, including galectin-3. Most treatment modalities in heart failure, however, are not acute interventions but chronic pharmacologic neurohormonal inhibition [47]. Further study is warranted, however, because it is currently unknown whether long-term treatments (eg, ACE inhibitors and aldosterone receptor blockers) intended to reduce matrix apposition and fibrosis lower galectin-3 levels.

If it is indeed proven that standard treatment of heart failure is associated with lowering of galectin-3 expression and levels, one could argue that galectin-3 itself could also be a target for therapy. Specific agents targeted against galectins have been tested in small trials with cancer patients. These agents have not been evaluated in experimental or clinical heart failure, but will likely soon be tested for their value in this devastating disease.

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