Chapter 5

Galectin-3 and Post-Myocardial Infarction Cardiac Remodeling

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ABSTRACT

This review summarizes the current literature regarding the involvement and the putative role(s) of galectin-3 in post-myocardial infarction cardiac remodeling. Post-myocardial infarction remodeling is characterized by acute loss of myocardium, which leads to structural and biomechanical changes in order to preserve cardiac function. A hallmark herein is fibrosis formation, both in the early and late phase following acute myocardial infarction. Galectin-3, a β-galactoside-binding lectin, which is a shared factor in fibrosis formation in multiple organs, has an established role in cardiac fibrosis in the setting of pressure overload, neuro-endocrine activation and hypertension, but its role in post-myocardial infarction remodeling has received less attention. However, accumulative experimental studies have shown that myocardial galectin-3 expression is upregulated after myocardial infarction, both on mRNA and protein level. This already occurs shortly after myocardial infarction in the infarcted and border zone area, and also at a later stage in the spared myocardium, contributing to tissue repair and fibrosis. This is associated with typical aspects of fibrosis formation, such as apposition of matricellular proteins and increased factors of collagen turnover. Interestingly, myocardial fibrosis in experimental post-myocardial infarction cardiac remodeling could be attenuated by galectin-3 inhibition. In clinical studies, circulating galectin-3 levels have been shown to identify patients at risk for new-onset heart failure and atrial fibrillation. Circulating galectin-3 levels also predict progressive left ventricular dilatation after myocardial infarction. We conclude that galectin-3 is an active player in cardiac remodeling after myocardial infarction. Future studies should focus on the dynamics of galectin-3 activation after myocardial infarction, and study the possibilities to target galectin-3.
INTRODUCTION

Myocardial infarction (MI) is a common complication of coronary artery disease (CAD). According to the World Health Organization, 7.3 million annual deaths worldwide are due to ischemic heart disease (IHD), making it the leading cause of death in developed countries (Mendis et al., 2011). With better treatment options, the death rate of IHD declined in most western countries, but in 2008 cardiovascular disease still accounted for one in three deaths in the USA (Roger et al., 2012).

MI is characterized by cardiomyocyte necrosis and acute loss of myocardial tissue, which leads to structural and biomechanical changes in order to preserve cardiac function and minimize diastolic and systolic wall stress. These changes include collagen deposition with scar formation, fibrosis, hypertrophy and modifications in ventricular architecture that encompass changes in the size, shape and composition of the left ventricle. These modifications, often referred to as ‘ventricular remodeling’, can profoundly affect the function of the ventricle and the patient’s prognosis (Eaton et al., 1979 and McKay et al., 1986). Especially large, transmural infarcts result in complex modifications in the ventricular architecture involving the infarcted as well as the non-infarcted myocardium. Experimental and clinical studies reveal that the degree and extent of remodeling over time is largely determined by the degree of accumulative myocardial injury (Chareonthaitawee et al., 1995 and van Gilst et al., 1996). Ventricular remodeling is a continuous process that starts early, but can last up to months or years, depending on infarct size, anatomic location, and local and systemic factors. The three major biomechanical mechanisms contributing to LV remodeling over time after myocardial infarction (MI) are: (1) early infarct expansion in the acute and sub-acute phase, that occurs during the days to weeks directly following MI (Kelley et al., 1999), (2) subsequent non-ischemic infarct extension into the adjacent non-infarcted region, during the weeks to months that follow MI (Ratcliffe, 2002) and (3) hypertrophy and dilatation of non-infarcted myocardium in the chronic phase, during months and years that follow MI (Kramer et al., 1998).

LV remodeling is the major determinant of survival after recovery from MI (White et al., 1987), and it has been strongly associated with clinical outcomes in numerous heart failure (HF) trials. In fact, evidence-based treatments that reduce mortality post-MI, as β-blockers and angiotensin converting enzyme (ACE) inhibitors, have been shown to inhibit LV remodeling (Abdulla et al., 2007). Therefore, modulation of ventricular remodeling is a very attractive option to prevent adverse clinical outcomes.
ROLE OF THE FIBROTIC RESPONSE TO INJURY

There is convincing and consistent evidence that the response to injury of cardiac, renal, lung, vascular, and liver tissue share a common pathway that is characterized by fibrotic changes in all of these tissues (Zeisberg and Kalluri, 2013). These fibrotic changes are a hallmark of organ dysfunction (Cui et al., 2013 and Koleganova et al., 2009).

Upon myocardial injury, cytokines are released by cardiomyocytes and activate several repair mechanisms. TGF-β1 is increased early in the infarcted area and activates macrophages, fibroblast chemotaxis and fibroblast proliferation (Desmouliere et al., 1993). Activated macrophages are capable of expressing ACE, leading to locally produced Angiotensin II that is regulated independently of plasma Angiotensin II but very important in reparative fibrosis (Desmouliere et al., 1993). The early release of different cytokines from injured cardiomyocytes also results in the transformation of fibroblasts into myofibroblasts, and subsequent expression of genes encoding for procollagens types 1 and 3, and generation of Angiotensin I and II, and the receptors for Angiotensin II, TGF-β1 and ET-1; which ultimately leads to an increased extracellular matrix production and substantial collagen turnover (Weber, 1997). Synthesis of collagens type 1 and 3 by myofibroblasts is modulated by several factors, including Angiotensin II, fibroblast growth factor, platelet-derived growth factor, ANP, and bradykinin-mediated prostaglandin E2 (Weber, 1997). Mechanical strain also determines the degree of collagen cross-linking and the strength of the fibrotic scar (McCormick et al., 1994).

Deposition of type III and type I collagens occurs predominantly in the infarcted tissue; however, it also occurs in non-infarcted myocardium when intercellular signaling is potentiated by stretch on the residual myocardium due to extensive cardiomyocyte necrosis. Type III collagen mRNA increases early post-MI and remains elevated for approximately 3 weeks; type I collagen mRNA increases also early but may remain elevated for at least 3 months (Cleutjens et al., 1995). Collagen in the infarcted myocardium is already detectable microscopically after 1 week and then increases dramatically; such that after one month the necrotic cardiomyocytes are entirely replaced by fibrotic tissue (Cleutjens et al., 1995). After scar formation is completed and the LV is able to cope with the wall stress, collagen formation is down-regulated and most myofibroblasts undergo apoptosis. Major advances have been made in the understanding of cardiac remodeling, the process that leads from initial assault to the heart, e.g. myocardial infarction, to end-stage HF (Sutton and Sharpe, 2000). Galectin-3 is a protein that gained interest because of its close relationship with fibrosis formation and as a new prognostic marker of HF.
GALECTIN-3

Galectin-3 is encoded by a single gene, LGALS3, which is located on chromosome 14, and consists of six exons and five introns (Raimond et al., 1997). It is a β-galactoside-binding lectin with two domains, namely an atypical N-terminal domain and a C-terminal carbohydrate-recognition domain (CRD) (Dumic et al., 2006). Galectin-3 is predominantly produced by macrophages, but many other cell types that have been described in the setting of myocardial infarction, produce galectin-3 as well, e.g. neutrophils, eosinophils, mast cells (Dumic et al., 2006) as well as fibroblasts (Yu et al., 2013). In response to circulating cytokines such as IL-4, part of the macrophages will differentiate towards the “alternative” phenotype (M2), and it is this macrophage phenotype that is characterized by the up-regulation of a number of genes such as the mannose receptor, that is important for galectin-3 production and function. (Mackinnon et al., 2008). Inflammation often precedes fibrosis and results in tissue damage and loss leading to enhanced fibrogenesis (Berk et al., 2007). By hitherto unexplained mechanisms, galectin-3 is secreted and can be measured in the blood stream. As such, galectin-3 has been evaluated as a biomarker, and was associated with HF severity (de Boer et al., 2009), and is a prognostic indicator in HF (Meijers et al., 2014a), as well as in patients with renal dysfunction (Drechsler et al., 2015; Meijers et al., 2014b). Currently, limited data is available regarding the association between circulating and tissue levels of galectin-3. In a recent study with 39 patients in hypertensive heart disease, it was described that there was no clear correlation between galectin-3 in the tissue and the plasma, which is comparable with other circulating fibrotic biomarkers (López et al., 2015).

GALECTIN-3 AND FIBROSIS/REMODELING

Galectin-3 is a shared factor in fibrosis formation in different organs. When secreted, galectin-3 acts on fibroblasts and initiates a pro-fibrotic program (Dumic et al., 2006). Mechanistically, in vitro galectin-3 turns quiescent fibroblasts into myofibroblasts that produce and secrete matrix proteins, including collagens, fibronectin, and TGF-β (Sharma et al., 2004). In vivo, several observations demonstrate the important role that galectin-3 has in cardiac fibrosis and remodeling. Sharma and colleagues (Sharma et al., 2004) showed in hypertensive rats that galectin-3 co-localizes in areas of fibrosis with macrophages and fibroblasts. Yu and colleagues (Yu et al., 2013) showed, again in hypertensive rats but also in mice subjected to pressure overload, that the absence of galectin-3 prevents cardiac fibrosis, and confirmed that galectin-3 is associated with αSMA staining (as a consequence of myofibroblast proliferation), proliferating cells, and fibrosis. Calvier and colleagues (Calvier et al., 2013) showed that galectin-3 was activated in aldosterone-induced cardiac fibrosis.
Specifically, \textit{in vivo}, galectin-3 is associated with fibroblast to myofibroblast differentiation, collagen synthesis, inflammation and renal epithelial-mesenchymal transition. The latter was observed during galectin-3 inhibition, which prevented a decrease of β-catenin and E-cadherin and an increase of fibronectin and αSMA in the kidney of aldosterone treated rats (Calvier et al., 2015). Genetic disruption of galectin-3 or pharmacological inhibition have consistently shown to reverse these endophenotypes, therefore, the association of galectin-3 with these phenomena does not merely appear to be associative, but rather causal. Besides cardiac fibrosis, galectin-3 plays a role in renal (Henderson et al., 2008 and Iacobini et al., 2005), hepatic (Henderson et al., 2006), vascular (Calvier et al., 2013 and Menini et al., 2013), and pulmonary fibrosis (Farnworth et al., 2008 and Mackinnon et al., 2012), and (genetic) disruption of galectin-3 attenuates fibrosis formation in all these organs (Henderson et al., 2006, Henderson et al., 2008, Mackinnon et al., 2012 and Yu et al., 2013). A schematic scheme of the function of galectin-3 is displayed in Fig. 1.

![Figure 1. The transition of fibroblast to myofibroblast and the involvement of galectin-3 leading to systolic and diastolic dysfunction.](image)

Circulating galectin-3 has emerged as a biomarker of fibrosis in heart and kidney disease, and increased baseline levels in healthy subjects are associated with mortality (de Boer et al., 2012 and Ho et al., 2012), and precede chronic kidney disease (O'Seaghdha et al., 2013). Furthermore, in prevalent HF, further increases of galectin-3 strongly predict poor outcome (Anand et al., 2013, Motiwala et al., 2013 and van der Velde et al., 2013). In 240 chronic HF patients wherein almost 70% had ischemic cardiomyopathy serial echocardiography was performed to analyze LV remodeling over time. Patients, in whom the LVEDV decreased over time, had significant lower levels of galectin-3 compared to patients with a stable LVEDV or an increase in LVEDV \((P=0.004)\). No significant differences in levels of NT-proBNP were observed in this study (Lok et al., 2013). However, few data are available on post-MI cardiac remodeling and therefore these data were summarized herein.
GALECTIN-3 AND POST-MYOCARDIAL INFARCTION CARDIAC REMODELING

Experimental studies
Sanchez-Mas et al. (2014) studied galectin-3 expression in cardiac tissue in rats after MI. In these rats, permanent ligation of the left anterior descending coronary artery was performed and rats were sacrificed at 1, 2, 4, 12 and 24 weeks post-MI. After MI, the rats showed a significant drop in left ventricle ejection fraction (LVEF) and their LV end-diastolic and end-systolic volumes were significantly increased during follow-up. Galectin-3 mRNA expression was increased in the infarcted area and reached a maximum at 1 week after MI, with a progressive decrease in the next weeks. Other fibrosis markers like collagen I, collagen III and TIMP-1 showed similar behavior as galectin-3. The non-infarcted area also showed an increased galectin-3 expression, but with a maximum peak at 24 weeks as schematically shown in Fig. 2. Collagen I, collagen III and TIMP-1 showed earlier peaks. Interestingly galectin-3 expression was correlated with macrophage infiltration, regardless of the area within the myocardium. This strengthens the evidence that macrophages are considered as the main source of galectin-3 (Sharma et al., 2004). In a very recent study in mice, mRNA and protein levels of galectin-3 were found to elevated, already 60 min and 30 min after MI (Hashmi and Al-Salam, 2014). To further explore involvement of galectin-3 in cardiac remodeling, galectin-3 knock-out mice were subjected to permanent coronary artery ligation and were compared to sham operated animals (Gonzalez et al., 2014). Interestingly, genetic disruption of galectin-3 showed a trend towards increased mortality (albeit non-significantly), and increased myocardial hypertrophy and (significantly) increased pulmonary congestion after one week after MI. This was associated with less fibrosis and macrophage infiltration in these animals. Evidence of adverse remodeling was present with increased ventricular dilation in the galectin-3 KO mice. Therefore, collectively these studies (Gonzalez et al., 2014, Hashmi and Al-Salam, 2014 and Sanchez-Mas et al., 2014) suggest that galectin-3 is an active participant in the remodeling process following MI. Apparently, in the earlier phases galectin-3 contributes to a reparative process in the infarcted area, which is essential for the maintenance of ventricular geometry and function in the first days after MI (Gonzalez et al., 2014). However, on longer term, chronic activation and tissue fibrosis adds to progressive remodeling, and galectin-3 is a contributor to this late phase.

Effects of MRAs on galectin-3-induced fibrosis
The rationale behind the use of mineralocorticoid receptor antagonists (MRAs) as a possible agent to prevent fibrosis formation is that aldosterone is a key player in fibrogenesis. Aldosterone is synthesized by myofibroblasts and has a higher concentration in the heart compared to plasma levels (Sun et al., 1994). Aldosterone stimulates transcription
Figure 2. Galectin-3 mRNA and protein levels after myocardial infarction at different time points (1, 2, 4, 12, and 24 weeks) in the infarcted and non-infarcted tissue (modified from: Sanchez-Mas et al., 2014).
of collagen type I and type III mRNA which can be inhibited via MRAs (Robert et al., 1999 and Silvestre et al., 1999).

Clinically, MRAs improve survival in patients with symptomatic chronic HF after MI (Maisel et al., 2014 and Pitt et al., 2003). Recently, it was shown that MRAs reverse cardiac and renal expression of galectin-3 in hypertensive rats (Calvier et al., 2015). Therefore MRAs may modify the biological activity of galectin-3 and subsequent LV remodeling. Lax et al. (2014) recently studied the effect of MRA treatment in a rat MI model (permanent ligation of the left anterior descending coronary artery). Rats were randomized into 4 groups (no treatment, eplerenone, spironolactone and sham operated) and sacrificed after 4 weeks. Galectin-3 gene expression was measured in the infarcted myocardium, as well as molecules involved in the galectin-3 signaling pathway (TGF-β and SMAD-3). MRA treatment (spironolactone or eplerenone) led to significantly lower expression of galectin-3, TGF-β and SMAD-3 in the infarcted myocardium at 4 weeks. Modulation of galectin-3 signaling by MRAs was correlated with lower myocardial fibrosis, by measuring it as collagen volume fraction and mRNA expression of Col I, Col III and TIMP-1; as well as lower inflammatory markers like TNF-alpha, IL-6 and MCP-1. In the non-infarcted myocardium of rats with MI, galectin-3 was also higher compared to the sham group but significantly lower than observed in the infarcted area, and at the time studied (4 weeks) was unaffected by MRAs. This study suggests that the well-established beneficial effects of MRAs after MI could, at least in part, be related to anti-fibrotic and anti-inflammatory properties linked to modulation of galectin-3 signaling, as molecular mechanism of MRA in post-MI remodeling. Of note, in this study the effect of MRAs on galectin-3 was observed after 4 weeks, which is later than the early phase of seven days where galectin-3 seem to have a reparative role (Sanchez-Mas et al., 2014). Together, the experimental evidence suggests that galectin-3 is involved in fibrotic and inflammatory processes in the weeks and months following MI, and that MRAs might interfere in these processes, and their benefits may at least in part be explained via galectin-3 modulation (Table 1).
Table 1: Main results experimental studies

| Study            | Species                  | Main results concerning galectin-3                                                                                                                                 |
|------------------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------
| Sanchez-Mas J.   | Rat; Wistar              | Infarcted area: increased mRNA and protein expression with max. at 1 week post-MI, with a progressive decrease in the next weeks. Non-infarcted area: mRNA expression significantly increased post-MI compared to sham group; with a late maximum at 6 months. Protein levels were similar to sham group in the first 4 weeks, with a late peak at 3 months post-MI. |
| Hashmi S.        | Mouse; C57Bl6/J          | Infarcted area: increased mRNA and protein expression at 60 min, 4 h, and 24 h post-MI compared to sham. Plasma Gal-3 levels were significantly raised at 24 h post-MI.                                                                                          |
| Gonzalez GE.     | Mouse; C57Bl6/J and Galectin-3 KO | Genetic deletion led to increased mortality, myocardial hypertrophy and pulmonary congestion in the acute phase of MI. Also adverse changes in early remodeling and ventricular function at 7 days post-MI were observed.                                           |
| Lax A.           | Rat; Wistar              | Infarcted area: increased protein expression post-MI and down-regulated with MRAs. Modulation of galectin-3 signaling induced by MRAs correlated with lower expression levels of fibrosis and inflammatory markers. Non-infarcted area: increased mRNA expression, but no signs of inflammation or fibrosis were observed. In the presence of MRAs, galectin-3 expression was unaffected. |

Clinical studies

From a clinical point of view, LV remodeling after MI is determined by the development of changes on myocardial function, shape and dilatation, leading to HF development. Galectin-3 has been extensively studied in HF (Filipe et al., 2015), but only a few clinical studies evaluated its effect on LV remodeling after MI; we provide an overview in Table 2.

One of the first studies that assessed the prognostic value of galectin-3 in STEMI patients undergoing primary percutaneous coronary intervention (pPCI) was conducted by Tsai et al. (Tsai et al., 2012). In this study, the FDA-cleared galectin-3 ELISA kit was not used and therefore it is impossible to compare galectin-3 values. Nevertheless, they found that high galectin-3 levels, 6 h after PCI, predicted 30-day major adverse clinical outcomes, including advanced CHF or 30-day death, independently and after adjustment for multiple vessel disease, LVEF and serum creatinin levels. Another study included 145 subjects with MI (Szadkowska et al., 2013) and found that galectin-3 levels, 3–5 days after acute MI, were not associated with LVEF (r: −0.003, P>0.05), but correlated with NT-proBNP (r: 0.27, P<0.001) and hsCRP (r: 0.20, P<0.05). During the hospitalization period, patients with elevated galectin-3 levels were more prone to develop new-onset AF and new-onset HF. In a very small sub-cohort of the occluded artery trial (37 patients) (Kruk et al., 2013), long-term follow-up measurements of galectin-3 were available. Concentrations of galectin-3 did not show significant changes comparing baseline (before PCI) to one-year follow-up (P=0.49).
Mayr et al. (2013) reported for the first time, the relation between infarct scar, left ventricular function and galectin-3 in patients after MI. Cardiac magnetic resonance (CMR) imaging with its concept of late enhancement provides high-resolution delineation of MI size as well as myocardial function. CMR and galectin-3 measurements were performed in 29 reperfused STEMI patients after four months. The correlation between galectin-3 and myocardial infarct size, although significant, was weak ($r = 0.406, P = 0.036$) and the correlation with LVEF was non-significant ($r = -0.349, P = 0.063$), these results however are not very robust due to limited sample size. In a larger cohort comprising 100 STEMI patients, CMR was performed at baseline and 4 months (Weir et al., 2013). Across the cohort, LVEF increased significantly between baseline and 4 months. Baseline galectin-3 was not correlated with baseline CMR measurements (LVEF $r = 0.14, P = 0.16$; infarct size $r = 0.10, P = 0.34$) but had an inverse correlation with LVEF at 4 months ($r = -0.25, P = 0.023$). NT-proBNP and the change of NT-proBNP over time was correlated with galectin-3 ($r = 0.30, P = 0.003$; $r = -0.24, P = 0.022$, respectively). Besides natriuretic peptides, galectin-3 was also significantly correlated with other ECM markers such as MMP-3, TIMP-1, MCP-1 and IL-8. In the same cohort, a possible association between higher galectin-3 levels
and more extensive remodeling was observed in patients with relatively preserved LV function early after MI but not in those with more severe LV dysfunction. In another study with patients 30 days post-MI, galectin-3 levels showed a non-significant trend to be associated with higher left ventricular filling pressures at rest ($P=0.062$) or at peak exercise ($P=0.18$) measured directly with pulmonary catheter or by echocardiography ($P=0.09$) (Andersen et al., 2014).

In the GIPS-III trial (Lexis et al., 2014), consisting of STEMI patients who underwent pPCI, 247 patients were studied in a biomarker analysis. Galectin-3 was an independent predictor for LVEF after 4 months. Elevated levels were correlated with a significant lower LVEF (van der Velde et al., 2014). Further clinical data are scarce and suggest a potential relationship between galectin-3 levels and higher risk of HF development after MI. However, findings are limited by the small sample size and the influence of the time of measurement after MI.

GALECTIN-3: A POSSIBLE TARGET FOR THERAPY

Galectin-3 as a target for therapy in HF has been tested in several animal models of HF, but in post-MI models, data are lacking. The anti-fibrotic tetra-peptide ac-SDKP was the first compound that showed to prevent the fibrotic effects of galectin-3 (Liu et al., 2009). A more direct link with galectin-3 in cardiac remodeling has been demonstrated by Yu et al. (2013) using mice that are genetically deficient for galectin-3. In this study, the galectin-3 knock-out mice and wild types were compared, undergoing different perturbations of cardiac stress, such as angiotensin II infusion or transverse aortic constriction. The galectin-3 knock-out mice had histologically less severe fibrosis formation, and more importantly, this resulted in improved hemodynamics—especially better LV relaxation, which is a marker of diastolic function.

We hypothesize that galectin-3 is inactivated when neutralizing ligands bind the CRD. Pectins, which have been most intensively studied in relation to galectin-3 inhibition, are believed to reduce the galectin-3 activity by binding to this CRD. Modified citrus pectin (MCP), an oligosaccharide present in the peels in fruits and vegetables, is the mostly studied pectin. The inhibitory effects have been observed in both heart failure, kidney disease (Kolatsi-Joannou et al., 2011), and liver disease. We make reference to a recent article that describes the potential mechanisms of galectin-3 inhibition (de Boer et al., 2014). In another study, MCP was shown to reduce collagen I production in an aldosterone-induced rat HF model (Calvier et al., 2013). Interestingly, MCP also showed to be an effective anti-fibrotic agent in acute renal injury model (Kolatsi-Joannou et al., 2011) and hypertensive nephropathy (Frenay et al., 2015). Collectively, these data suggest that galectin-3 may effectively be targeted. Currently, clinical trials are being...
conducted to investigate the potential function of pectins in HF (MCP in patients at risk for heart failure, ClinicalTrials.gov identifier NCT01960946). Another galectin-3 inhibitor and potential therapeutic option is N-acetyllactosamine (N-Lac) which was studied in Ren2 rats, a model for “hypertensive cardiomyopathy” (Yu et al., 2013). N-Lac treated Ren2 rats had preserved fractional shortening and untreated Ren2 rats had increased LVEDP and increased lung weights, a sign of congestion. Accelerated cardiac remodeling in untreated Ren2 rats was associated with poorer survival compared to SD (control) rats, N-Lac treated rats had a better survival. In another transverse aortic constriction experiment, mice were treated with N-Lac, and showed no progressive remodeling compared to appropriate controls.

There are no convincing data to suggest that contemporary post-MI treatment, such as statins, aspirin, β-blockers, ACE inhibitors or mineralocorticoid receptor antagonists may be guided by galectin-3 levels. Weir et al. showed that response to the eplerenone could not predicted by galectin-3 (Weir et al., 2013). At this stage it is still speculative to decide if, and which patients could benefit from galectin-3 inhibition. Post-MI remodeling is needed for the adaptive response of the cardiac muscle to cope with the tissue and functional loss. However the maladaptive remodeling, involving excessive built-up of fibrosis and collagen deposition should be considered as a target for inhibition, possibly via galectin-3. van der Velde et al. (2014) identified patients with elevated galectin-3 at baseline who were at risk for lower LVEF after four months. These patients would be putative candidates for galectin-3 inhibition, arguably after the early expansion of the myocardial infarction (3–4 weeks).

**CONCLUSION**

Galectin-3 has been associated with fibrosis development and cardiac remodeling, hallmarks of HF. Fibrosis and scar formation are crucial in early and late remodeling following MI and several experimental studies have shown that myocardial galectin-3 expression is up-regulated after MI. In addition, clinical studies suggest a link between higher circulating levels of galectin-3 and a HF-prone phenotype after MI. However, we cannot simply identify galectin-3 as a good or bad player, because of the complex sequel of events in post-MI remodeling. It may be that in the early phase, when tissue repair is warranted, galectin-3 activation is necessary for the heart to cope with the excessive stress. At a later stage, ongoing activation of reparative mechanisms may become detrimental, and galectin-3 acts during this process too. During this later phase we believe galectin-3 could be a target for therapy. More in-depth mechanistic studies are needed to precisely describe the potential role of galectin-3 in post-myocardial remodeling.
REFERENCES


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