Review

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Galectin-3 in diabetic patients

Abstract: Galectin-3 is a versatile molecule which exerts several and sometimes opposite functions in various pathophysiological processes. Recently, galectin-3 has gained attention as a powerful predictor of heart failure and mortality, thus becoming a useful prognostic marker in clinical practice. Moreover, though not specifically investigated in diabetic cohorts, plasma levels of galectin-3 correlated with the prevalence of diabetes and related metabolic conditions, thus suggesting that pharmacological blockade of this lectin might be successful for treating heart failure especially in subjects suffering from these disorders. Indeed, galectin-3 is considered not only as a marker of heart failure, but also as a mediator of the disease, due to its pro-fibrotic action, though evidence comes mainly from studies in galectin-3 deficient mice. However, these studies have provided contrasting results, with either attenuation or acceleration of organ fibrosis and inflammation, depending on the experimental setting and particularly on the levels of advanced glycation endproducts (AGEs)/advanced lipoxidation endproducts (ALEs), of which galectin-3 is a scavenging receptor. In fact, under conditions of increased AGE/ALE levels, galectin-3 ablation was associated with tissue-specific outcomes, reflecting the AGE/ALE-receptor function of this lectin. Conversely, in experimental models of acute inflammation and fibrosis, galectin-3 deficiency resulted in attenuation of tissue injury. There is a need for prospective studies in diabetic patients specifically investigating the relation of galectin-3 levels with complications and for further animal studies in order to establish the effective role of this lectin in organ damage before considering its pharmacological blockade in the clinical setting.

Keywords: advanced glycation endproducts; advanced lipoxidation endproducts; diabetes; fibrosis; galectin-3; inflammation; receptor for advanced glycation endproducts (RAGE).

Introduction

Galectin-3 is a member of an evolutionarily conserved family of soluble β-galactoside-binding lectins. The structure of this 29- to 35-kDa protein consists of two domains, the C-terminal carbohydrate recognition domain (CRD), with highly conserved residues between members of the family, and the N-terminal domain, with a unique short end continuing into an intervening proline-glycine-alanine-thyrosine-rich (PGAY) repeat motif [1] (Figure 1).

Galectin-3 expression in tissues appears to be developmentally-regulated, being more abundant during embryogenesis and development than in adult life, when it is detected in various epithelial cells, cartilage and bone as well as in inflammatory cells, either constitutively or in an inducible fashion [2, 3].

Galectin-3 shows a ubiquitous localization within the cell and is also secreted into the extracellular space, although it lacks a signal sequence for transfer into the endoplasmic reticulum and Golgi compartments and entry into classical secretory pathways [4]. This dual localization of galectin-3 determines two different modes of interaction with proteins. Extracellular galectin-3 interacts via the CRD [5] with the β-galactoside residues of several extracellular matrix (ECM) and cell surface glycoproteins [6]; this is the classical lectin-glycoconjugate interaction. Conversely, interactions of intracellular galectin-3 occur via peptide-peptide associations mediated by its N-terminus domain, though also the CRD may be involved at this level [7]. These structural properties enable galectin-3 to bind several proteins, thus exerting multiple functions.
which make it a broad-spectrum biological response modifier involved in several disease conditions [8] (Figure 1).

Intracellularly, galectin-3 acts as a pre-mRNA splicing factor [9] and regulates the cell cycle [10] by modulating cell proliferation, death, and differentiation. Galectin-3 promotes cell proliferation [11, 12] and favors cell survival by protecting from apoptosis induced by a variety of death signals [12, 13]. By virtue of its pro-proliferative and anti-apoptotic action, galectin-3 is considered as an immediate early gene possibly implicated in tumor growth [14]. However, galectin-3 can also be pro-apoptotic and mediate T cell and neutrophil death [15]. Extracellularly, galectin-3 regulates cell adhesion in a dual manner. Cell surface galectin-3 promotes homo- and heterotypic cell-to-cell interactions by serving as a cross-linking bridge between adjacent cells [16, 17], whereas it down-regulates cell adhesion to the ECM component laminin via an association with the α1β1-integrin receptor [18, 19]. This dual function of galectin-3 on cell adhesion has made this lectin an interesting target for the study of tumor progression and invasiveness [20].

Another important function of (extracellular) galectin-3 is the modulation of immune/inflammatory function, with both pro- and anti-inflammatory actions, depending on multiple factors, such as type of inflammatory setting and target cell/tissue [8]. Finally, galectin-3 facilitates repair of tissue injury by promoting fibrogenesis [21].

Recently, galectin-3 has gained attention as a powerful predictor of heart failure and mortality, thus becoming a useful prognostic marker in clinical practice. Indeed, galectin-3 is considered not only as a disease marker, but also as a mediator of the development and progression of heart failure [22]. In fact, since fibrosis is one of the main mechanisms underlying increased ventricular stiffness and diastolic dysfunction [23], the pro-fibrotic and immune-modulatory properties of galectin-3 have been claimed to explain the association between plasma levels of this lectin and the presence and severity of heart failure [24]. This interpretation is consistent with the finding that galectin-3 was significantly correlated with serum markers of cardiac ECM turnover in patients with heart failure [25].

Moreover, though not specifically investigated in large diabetic cohorts, plasma levels of galectin-3 correlated with the prevalence of diabetes and the other diseases conditions clustering in the metabolic syndrome [22], thus suggesting that pharmacological blockade of this lectin might be successful for treating heart failure especially in subjects with metabolic disorders.

However, studies in galectin-3 knockout animals have provided contrasting results, with either attenuation or acceleration of organ fibrosis and inflammation, depending on the experimental setting and particularly on the levels of advanced glycation endproducts (AGEs)/advanced lipoxidation endproducts (ALEs), of which galectin-3 is a scavenging receptor. In fact, under conditions of increased AGE/ALE levels, galectin-3 ablation was associated with tissue-specific outcomes, reflecting the AGE/ALE-receptor function and possibly the direct anti-inflammatory effects of this lectin [7]. Conversely, in experimental models of acute inflammation and fibrosis, deletion of Lgals3 gene resulted in prevention or attenuation of target tissue injury [21].

This article will briefly review the evidence supporting the prognostic value of galectin-3 in clinical settings and experimental data on the role of this lectin as a disease mediator.

Galectin-3 as a marker of heart failure morbidity and mortality: human studies

A large body of evidence from studies from both community-based cohorts and selected populations has linked galectin-3 plasma levels with presence and severity of heart failure and all-cause and cardiovascular death.

Data from the general population come from 7968 subjects from the Prevention of Renal and Vascular End-stage Disease (PREVEND) study and 3535 participants in the Framingham Offspring Cohort. The first study showed a strong relationship of galectin-3 plasma levels with death, though only the association with all-cause
mortality remained significant after adjustment for traditional and non-traditional risk factors [26]. Likewise, in the second survey, galectin-3 levels were independently associated with an increased risk for incident heart failure and all-cause mortality, even after adjustment for clinical variables and brain natriuretic peptide (BNP) [27].

Several studies have addressed the relation between galectin-3 and heart failure in subjects suffering from this disease condition, either acute or chronic, with and without preserved left ventricular ejection fraction (LVEF). In 599 patients presenting with dyspnea at the emergency department, galectin-3 levels were significantly higher in subjects with heart failure (209, 35%) than in those without. Moreover, though inferior to levels of amino-terminal pro-BNP (NT-proBNP) for diagnosis of heart failure, elevated galectin-3 concentration was the best independent predictor of mortality or the combination of death/recurrent heart failure within 60 days. Finally, Kaplan-Meier analyses showed that the combination of an elevated galectin-3 with NT-proBNP was a better predictor of mortality than either of the two markers alone [28]. In a nested case-control study among patients with acute coronary syndrome from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial, baseline galectin-3 levels showed a graded relationship with risk of acute heart failure, which remained significant when adjusted for hypertension, diabetes, and prior myocardial infarction and heart failure, though it was attenuated when BNP was added to the model [29]. In 592 subjects with chronic heart failure from the Coordinating study evaluating outcomes of Advising and Counseling in Heart failure (COACH) trial, baseline galectin-3 levels were independently associated with a composite of all-cause mortality and hospitalization for heart failure. While serial measurements of galectin-3 did not appear to add to the prognostic power of single measurements, the predictive value of plasma galectin-3 was stronger in heart failure patients with preserved than in those with reduced LVEF and increased when combined with BNP levels [30]. In the Valsartan Heart Failure Trial (Val-HeFT), the increases in galectin-3 over time, but not baseline levels, were independently and significantly associated with risk of all-cause mortality, first morbid event, and hospitalizations for heart failure, even after adjusting for all the clinical and biochemical baseline and serial change variables including estimated glomerular filtration rate (eGFR) and NT-proBNP [31]. Conversely, a combined analysis of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) and COACH trial showed that increasing galectin-3 levels over time, from a low to high galectin-3 category, were associated with significantly more heart failure hospitalization and mortality compared with stable or decreasing galectin-3 levels [32].

At variance with the above reported studies, the association between galectin-3 levels and hospitalization-free survival did not persist after adjustment for other predictors, especially NT-proBNP, in the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) [33]. Moreover, in older patients with advanced chronic systolic heart failure of ischemic etiology from the CORONA, elevated galectin-3 levels were not associated with the composite outcome of cardiovascular death, non-fatal myocardial infarction, or stroke when adjusting for NT-proBNP [34], though they predicted response to statin therapy [35]. Finally, a recent retrospective analysis of 119 patients showed that galectin-3 levels were similarly elevated in all patients with heart failure, regardless of whether it was acute or chronic or systolic or diastolic in nature. Moreover, galectin-3 levels in patients with heart failure correlated with NT-proBNP, but this relationship was significantly attenuated after adjustment for age and eGFR. Conversely, the relationship between galectin-3 levels and eGFR persisted after corrections for age, LVEF, and NT-proBNP and did not vary according to the presence of heart failure [36]. These results suggest that the prognostic role of galectin-3 in heart failure may be related as much to renal impairment as to cardiac dysfunction [37]. Indeed, a recent longitudinal analysis of 2450 participants in the Framingham Offspring Cohort showed that elevated galectin-3 at baseline predicts a rapid decline in eGFR and a higher risk of incident chronic kidney disease, but not of incident albuminuria [38], consistent with a previous study reporting an association of high plasma galectin-3 levels with renal insufficiency and poorer survival in patients with chronic systolic heart failure [39].

In samples from the general population, circulating galectin-3 levels correlated with age, female gender, and markers of inflammation and target organ damage, but also with prevalence of diabetes, obesity, hypertension, and hypercholesterolemia and levels of components of the metabolic syndrome [26, 27]. Moreover, galectin-3 levels were found to be higher in subjects with obesity or type 2 diabetes [40] and a cross-sectional survey showed that high galectin-3 values were associated with micro- and macrovascular complications in diabetic patients [41]. Thus, the higher galectin-3 levels in diabetic individuals and in general in those with dysmetabolic disorders might mark the increased susceptibility of these subjects toward heart failure, though longitudinal studies of adequate size and duration specifically testing this hypothesis are needed.
Galectin-3 as a disease mediator: animal studies

The human studies showed that galectin-3 is a powerful predictor of the development and progression of heart failure and suggested that this might be the case especially in high-risk individuals, such as subjects with diabetes and other metabolic disorders. However, these studies did not provide conclusive evidence that galectin-3 plays a role of mediator in the setting of heart failure. Thus, the concept that galectin-3 is causally implicated in the development of this condition is still based on data from experimental animal models showing that this lectin is involved in organ fibrosis.

Several rodent models of pressure overload [42–44] and aortic constriction [44] exhibited increased myocardial and vascular expression of galectin-3. Moreover, infusion of this lectin in pericardial sac of normal rats induced myocardial fibrosis and left ventricular dysfunction [42, 45], which were prevented by the galectin-3 blocker N-acetyl-seryl-aspartyl-lysyl-proline [45]. Other inhibitors of galectin-3, modified citrus pectin and N-Lac, respectively, prevented vascular fibrosis induced by aldosterone [43] and cardiac remodeling occurring in both homozygous transgenic TGRmRen2-27 (Ren-2) rats and mice subjected to transverse aortic constriction [44]. Finally, galectin-3 deficient mice were protected from the pro-fibrotic effects of aldosterone treatment [43] and transverse aortic constriction [44].

Galectin-3 ablation has been shown to result in attenuation of fibrosis also in other organs, such as the kidney, lung and liver, when subjected to specific pro-fibrotic stimuli. In fact, tubular atrophy and interstitial fibrosis after renal transplantation [46], renal tissue damage triggered by ischemia and reperfusion injury [47] and renal fibrosis induced by unilateral ureteric obstruction [48, 49] were attenuated by deletion of Lgals3 gene. Likewise, in two well-characterized rodent models of lung fibrosis, adeno-viral transforming growth factor (TGF)-β1 and bleomycin-induced, lesions were dramatically reduced in mice deficient in galectin-3 [47, 50]. This was associated with reduced TGF-β1-induced epithelial to mesenchymal transition (EMT) as well as myofibroblast activation and collagen production, both in vivo and in vitro [46]. Similar results were obtained in the bleomycin-induced lung fibrosis model with an inhibitor of galectin-3, TD139 [47]. Finally, galectin-3 disruption attenuated ECM production both in vitro, in hepatic stellate cell cultures, and in vivo, in the model of CCL4-induced cirrhosis, again through blockade of TGF-β-mediated myofibroblast activation [51]. Also liver fibrosis and cirrhosis induced by thioacetamide were reversed by two galectin-3 inhibitors, GR-MD-02 (galactoarabino-hamnoglacturonan) and GM-CT-01 (galactomannan) [52].

Though the pro-fibrotic effect of galectin-3 is often related to its pro-inflammatory action, this lectin was shown to directly mediate transdifferentiation into collagen-producing cells, thus leading to organ fibrosis. Maeda et al. showed that galectin-3 induced hepatic stellate cells transdifferentiation into myofibroblasts via the mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK)–ERK 1/2 signaling pathway and, at variance with galectin-1, in a protein kinase C- and A-dependent manner [53], whereas MacKinnon et al. showed that galectin-3 ablation reduced alveolar epithelial cell EMT in response to TGF-β1 [50]. In addition, galectin-3 plays a complex role in the modulation of immune/inflammatory function, with distinct pro-inflammatory actions, but also with relevant anti-inflammatory effects which predominate under chronic conditions [7]. In acute settings, galectin-3 favors the inflammatory response against microbial infections. It is involved in the initiation phase (chemoattraction of monocytes and macrophages, adhesion of neutrophils to laminin and endothelial cells, recognition of microbes) [54–56], the induction of cellular effector functions (respiratory burst in neutrophils and monocytes with reactive oxygen species production, phagocytosis) [57–60], and the modulation of apoptotic cell death [57, 61]. It also participates in allergic reaction by inducing mediator release by mast cells [62]. Consistently, studies in galectin-3 deficient mice with experimentally-induced peritonitis have provided strong evidence of its pro-inflammatory effects [63]. However, under chronic conditions, galectin-3 appears to favor the resolution of inflammation, thus limiting tissue injury and promoting repair. In fact, it inhibits lipopolysaccharide-mediated inflammation [64], promotes T-cell apoptosis [65] and negatively regulates TCR-mediated T-cell activation [66, 67]. Moreover, MacKinnon et al. have shown that up-regulation of galectin-3 expression is a feature of the alternative macrophage (M2) phenotype and that release of galectin-3 by alternatively activated macrophages sustains the M2 phenotype contributing to some of its functions in vivo [68]. For instance, Karlsson et al. showed that galectin-3, by functioning as an opsonin, favors the phagocytic clearance of apoptotic neutrophils by macrophages, a process of crucial importance for termination of acute inflammation [69]. Accordingly, Cabero et al. have recently demonstrated that galectin-3 is a legitimate MerTK-specific “eat-me” signal which stimulates phagocytosis of apoptotic cells and cellular debris [70]. Finally, endothelial galectin-3 might also play a role in chronic inflammatory
conditions, such as atherosclerosis and related cardiovascular events, since it was shown that its up-regulation is part of the vascular response to diabetes [71] and that, together with galectin-1, galectin-3 is a partner for von Willebrand factor (VWF), participating in the modulation of VWF-mediated thrombus formation [72]. Consistently, the absence of galectin-1 and galectin-3 is associated with more efficient formation of platelet-decorated VWF strings along the endothelial surface and with enhanced formation of arterial thrombi [72].

In addition to exerting direct anti-inflammatory effects, galectin-3 has also been shown to attenuate inflammation by serving as a “scavenger” receptor for AGEs and ALEs via induction of their internalization and removal [73], at variance with receptor for AGEs (RAGE), which mediates the injurious effect of these byproducts [74]. A galectin-3-deficient mouse model has been used to investigate the role of this lectin in retinal, renal, vascular, and liver tissue injury under various experimental conditions of increased AGE/ALE levels, such as streptozotocin-induced diabetes, normal aging, injection of the AGE/ALE N′-carboxymethyllysine (CML)-modified mouse serum albumin, and feeding with a pro-atherogenic high fat diet (HFD).

Lgals3 gene deletion effectively prevented early retinal changes associated with streptozotocin-induced diabetes [75], whereas it abolished the AGE-mediated increase in retinal ischemia and restored the neovascular response to that seen in controls [76].

Galectin-3 ablation resulted in accelerated diabetes-induced glomerulopathy, as shown by the more marked glomerular lesions and the significantly higher increase in albuminuria and mesangial expansion, the functional and structural hallmarks of glomerulopathy [77]. Moreover, both circulating and renal tissue levels of AGEs increased more markedly in response to diabetes and renal cortex RAGE expression was up-regulated even in control animals and increased in a significantly higher extent in diabetic mice. Similar features of more marked fibrosis and inflammation were observed in the aging [78], AGE-injection [79], and HFD [80] models.

Likewise, galectin-3 deficient animals showed accelerated atherosclerosis when fed a HFD, with a higher lesion area and length and particularly with development of complex lesions, as compared with the simple fatty streaks observed in the wild-type mice. This was also associated with increased aortic levels of the AGES/ALEs CML and protein adducts of 4-hydroxy-2-nonenal and expression of RAGE, and with unique inflammatory features with a more marked infiltration of monocytes/macrophages and, particularly, with the presence of an extensive infiltrate of T lymphocytes with predominant Th-1 phenotype, as shown by CD3 and CXCR3 staining [81]. In contrast to these findings, two independent studies conducted in ApoE-null mice, a mouse model of atherosclerosis, have suggested a pathogenic role of galectin-3. In the first study, Nachtigal et al. showed that ApoE null mice on a standard chow develop attenuated atherosclerosis when crossbred with galectin-3 deficient mice [82]. A possible explanation for this difference is that, at variance with the study of Iacobini et al. [81], while the wild-type mice were on a C57BL/6J background, the galectin-3 deficient mice were on a mixed background between C57BL/6J and 129/SvEv, a strain which has long been recognized to be less prone to develop atherosclerotic lesions than the C57BL/6J [83, 84]. In the second study, MacKinnon et al. have also reported that galectin-3 ablation decreases atherosclerosis in ApoE-null mice fed a high-cholesterol Western diet [85]. However, in contrast with the reduced atherosclerotic burden, and consistently with data obtained by Iacobini et al., galectin-3 ablation induced a less stable plaque phenotype, characterized by reduced M2 macrophages polarization and decreased collagen content [85]. A final consideration about these apparently conflicting findings is that results in double knockout mice could be related to yet unknown specific interactions between the two genotypes.

In contrast with findings in the kidney and the aorta, where galectin-3 ablation was associated with an exacerbation of the disease [77–81], in the liver of the same animals, HFD-induced non-alcoholic steatohepatitis (NASH) was attenuated by galectin-3 ablation, as indicated by the lower extent of inflammation and fibrosis, the two hallmarks of NASH. Consistently, liver AGE and ALE levels and RAGE expression were decreased in galectin-3 deficient mice as opposed to wild-type. Moreover, galectin-3 silencing reduced the uptake of the AGE CML by liver sinusoidal endothelial cells, the main site of AGE removal, thus indicating that this lectin [86], at variance with scavenger receptor A and CD36 [87, 88], is a major scavenger receptor in the liver. Therefore, in galectin-3 deficient mice, the reduced hepatic uptake of AGEs/ALES could have played a role both in the prevention of NASH and the increase of circulating levels of these byproducts. These studies demonstrated that lesions were accelerated in tissues where galectin-3 ablation was associated with increased tissue AGE/ALE deposition and consequent RAGE overexpression (i.e., in the kidney and aorta) and attenuated where the absence of this lectin resulted in reduced ALE/ALE accumulation, with lack of stimulation of RAGE expression (i.e., in the liver). This prompted the hypothesis that galectin-3 plays a supportive role in the
pathogenesis of complications of metabolic disorders, i.e., a role which is exerted through a dual, tissue-specific modulation of RAGE expression, depending on the anabolic or catabolic role of the tissue in the metabolism of AGEs/ALEs. This view is supported by the observations that diabetic glomerulopathy was accelerated in transgenic mice over-expressing RAGE [89]; diabetes-induced atherogenesis was attenuated in ApoE null mice by RAGE blockade with soluble RAGE [90]; and liver fibrosis induced by administration of carbon tetrachloride to normal rats was ameliorated by RAGE silencing [91]. However, some AGE/ALE- and RAGE-independent effects of galectin-3 might also be claimed to explain these findings, especially the direct anti-inflammatory effect of this lectin at the aortic level, and the pro-fibrotic action at the hepatic level (Figure 2). In particular, the distinct inflammatory features of galectin-3 deficient animals at the aortic and renal level may be explained also by the lack of direct anti-inflammatory actions of this lectin. Likewise, the lack of the pro-fibrotic effect of galectin-3 may have participated in the attenuation of NASH and, together with the impaired clearance of apoptotic cells favored by the deficiency of this lectin, to the enlargement of the necrotic core and thinning of the fibrous cap in plaques.

Finally, recent evidence suggests that galectin-3 might be also involved in the regulation of glucose homeostasis by acting at the level of adipose tissue and pancreatic islets, thus participating in the pathogenesis of obesity and type 2 diabetes. Two independent research laboratories investigated the role of galectin-3 in the modulation of metabolic disorders induced by an obesogenic HFD containing 60% calories from saturated fat [92, 93]. Both studies demonstrated a protective role of galectin-3 toward obesity and type 2 diabetes, via modulation of the responsiveness of innate and adaptive immunity to over-nutrition [92, 93]. Also in both studies, increased adiposity and inflammation at the visceral adipose tissue (VAT) and systemic level were associated with altered glucose homeostasis, as evidenced by increased fasting glucose and glycated hemoglobin levels [92, 93]. Moreover, Pejnovic et al. [92] showed that, in galectin-3 deficient mice fed a HFD, impaired glucose metabolism was associated with a more marked insulin resistance, as assessed by the HOMA-IR, at variance with findings from Pang et al. [93]. In addition to VAT, Pejnovic et al. found increased inflammation also in pancreatic islets from galectin-3 deficient mice fed a HFD, as demonstrated by a marked infiltration of cells of the macrophage/dendritic lineage with various degrees of insulitis [92]. These authors also showed that galectin-3 deficient mice fed a HFD had increased accumulation of AGEs in the islets [92], a finding in keeping with the AGE-receptor function of galectin-3, which favors AGE degradation [7]. These data indicate an important role of galectin-3 in protecting islets from inflammation and injury induced by a variety of stimuli associated with overfeeding, including AGEs. This view is also consistent with the finding that the circulating levels of galectin-3 observed in patients with type 2 diabetes correlate positively with body mass index and negatively with glycated hemoglobin [40].

### Conclusions

Existing literature indicates that galectin-3 is a versatile molecule serving as a broad-spectrum biological response modifier. As a consequence, it exerts numerous and sometimes opposite functions.

On the grounds of human studies addressing the role of galectin-3 as a marker of morbidity and mortality for heart failure, this lectin should be considered as a “bad-guy” and, hence, amenable of pharmacological blockade. However, studies conducted in vitro and in experimental animal models of diabetes have indicated that it might be a “good-guy” by virtue of its participation in the endothelial response to diabetes, regulation of thrombus formation, and modulation of the immune/inflammatory system. In general, factors involved in determining the final outcome favored by galectin-3 are the type of injurious stimulus, the context of organ damage, and the cellular localization.
of this lectin. In particular, in diabetic subjects, galectin-3 plays different roles, either dependent on or independent from its AGE/ALE binding function. Moreover, ALE/AGE-dependent effects of galectin-3 vary among different organs, reflecting tissue differences in the function of the ALE/AGE receptor system, which, in the liver, is mainly implicated in ALE/AGE removal from circulation and detoxification. Therefore, although most of the studies agree in considering galectin-3 as a marker of inflammation and fibrosis, studies on experimental animal models of metabolic disorders suggest that the increased expression of galectin-3 may be part of an adaptive response to tissue injury, favoring resolution of inflammation and opposing to chronification of the inflammatory process. Consistently, galectin-3 ablation induces a pro-inflammatory phenotype characterized by an increased systemic, pancreatic and VAT inflammatory response to metabolic stimuli and an exacerbated vascular and renal tissue damage induced by diabetes and related disorders.

Based on these considerations, there is the need of large, prospective studies specifically investigating the relation of plasma levels of galectin-3 with long-term complications in diabetic patients. However, prior to investigating the effect of selective inhibitors of circulating galectin-3 in diabetic and non-diabetic patients, further research on animal models is required in order to establish whether this lectin is a mediator of organ damage, a simple bystander, or a protective agent in these chronic stimuli and an exacerbated vascular and renal tissue injury, favoring resolution of inflammation and opposing to chronification of the inflammatory process.

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