Galectin-3 as a novel biomarker for disease diagnosis and a target for therapy (Review)

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Abstract. Galectin-3 is a member of the galectin family, which are β-galactoside-binding lectins with ≥1 evolutionary conserved carbohydrate-recognition domain. It binds proteins in a carbohydrate-dependent and -independent manner. Galectin-3 is predominantly located in the cytoplasm; however, it shuttles into the nucleus and is secreted onto the cell surface and into biological fluids including serum and urine. It serves important functions in numerous biological activities including cell growth, apoptosis, pre-mRNA splicing, differentiation, transformation, angiogenesis, inflammation, fibrosis and host defense. Numerous previous studies have indicated that galectin-3 may be used as a diagnostic or prognostic biomarker for certain types of heart disease, kidney disease and cancer. With emerging evidence to support the function and application of galectin-3, the current review aims to summarize the latest literature regarding the biomarker characteristics and potential therapeutic application of galectin-3 in associated diseases.

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1. Introduction

Galectins are a family of β-galactoside-binding lectins with ≥1 evolutionary conserved carbohydrate-recognition domain (CRD) (1). At present, 15 galectins have been identified in mammals, and are divided into three types based on domain organization as follows: i) Prototype galectins with one single CRD; ii) tandem-repeat galectins with two CRDs; iii) chimera-type galectins with a single CRD connected to a long, flexible N-terminal domain (1-3). Note that Galectin-3 is the only chimera-type galectin. Human galectin-3 is a 35-kDa protein that is coded by a single gene, LGALS3, located on chromosome 14. The N-terminal domain of galectin-3 is essential for its multimerization, sensitive to proteolysis by matrix metalloproteinases and may participate in the interaction with other intracellular proteins (3). Furthermore, the first 12 amino acids of galectin-3 are necessary for its secretion and nuclear translocation (4,5). The C-terminal CRD of galectin is responsible for its interaction with glycoconjugates containing N-acetyllactosamine. Thus, galectin-3 binds proteins in a carbohydrate-dependent and -independent manner.

Galectin-3 is widely expressed in human tissues, including all types of immune cell (macrophages, monocytes, dendritic cells, eosinophils, mast cells, natural killer cells, and activated T and B cells), epithelial cells, endothelial cells and sensory

Abbreviations: CRD, carbohydrate-recognition domain; HF, heart failure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HFpEF, HF patients with a preserved ejection fraction; HFrEF, HF patients with a reduced ejection fraction; LVAD, left ventricular assist device; LV, left ventricular; sST2, soluble suppression of tumorigenicity 2; BNP, B-type natriuretic peptide; CHD, coronary heart disease; MI, myocardial infarction; AF, atrial fibrillation; STEMI, ST-elevated myocardial infarction; pPCI, primary percutaneous coronary intervention; IL, interleukin; HT, heart transplantation; ARF, acute renal failure; CKD, chronic kidney disease; HD, hemodialysis; RCC, renal cell carcinoma; PTC, papillary thyroid carcinoma; HBME-1, Hector Battifora mesothelial epitope-1; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis

Key words: galectin-3, tumor biomarker, heart disease
neurons (3,6). The expression of galectin-3 in tissues is developmentally regulated; it is more abundant during embryogenesis and development compared with adult life (7). Furthermore, during the early stages of embryogenesis, its expression pattern is more specific, located predominantly in the epithelia, kidney, chondrocytes and liver (8). However, galectin-3-knockout mice are viable without obvious abnormalities with the exception of premature senescence (9,10).

Galectin-3 is predominantly located in the cytoplasm and shuttles into the nucleus (Fig. 1). In addition, it is secreted to the cell surface and into biological fluids (3). The different locations of galectin-3 contribute to its various functions. In the cytoplasm, galectin-3 is important for cell survival, due to its interaction with certain survival-associated proteins, including B-cell lymphoma-2 (Bcl-2) and activated guanosine-5'-triphosphate (GTP)-bound K-Ras. In the nucleus, galectin-3 promotes pre-mRNA splicing and regulates gene transcription, whereas extracellular galectin-3 modulates cell-cell interactions, including between epithelial cells and the extracellular matrix. Thus, it is involved in cell differentiation, inflammation, fibrogenesis and the host defense (3,11). Therefore, galectin-3 is pivotal in numerous biological activities including cell growth, apoptosis, pre-mRNA splicing, differentiation, transformation, angiogenesis, inflammation, fibrosis and host defense. Previous evidence has indicated that galectin-3 is involved in the pathogenesis of cardiovascular remodeling, as well as in various autoimmune and inflammatory processes (2,6,7,12-18).

A total of 97.5% of the galectin-3 reference population was 27.5 ng/ml according to the product insert of an ARCHITECT Galectin-3 assay (www.abbottdiagnostics.com). Both increased and decreased expression levels of galectin-3 are observed in various types of disease including heart, renal and liver disease, cancer and infections. Furthermore, galectin-3 is a stable biomarker and is not associated with age, body mass index or sex (19,20). Furthermore, galectin-3 does not exhibit circadian variation and increases marginally following exercise, returning to normal levels after 1-3 h (21). Therefore, galectin-3 may be used in the diagnosis and prognosis of various types of disease, and therefore may also serve as a therapeutic target for treating disease. Despite several reviews commenting on these uses, numerous studies have been published in the last 3 years and provided certain novel ideas, particularly for the use of galectin-3 in humans. Thus, the present review summarizes the current literature, regarding biomarker characteristics and possible therapeutic applications of galectin-3 in disease.

2. Galectin-3 and cardiovascular disease

Elevated serum galectin-3 levels have been detected in almost all types of cardiovascular disease and its prognostic value for different clinical outcomes has been extensively investigated in patients (Table I).

*Heart failure (HF).* Galectin-3 as a biomarker of fibrosis and inflammation has been implicated in the development and progression of HF, and may predict increased morbidity and mortality. Two recent meta-analyses demonstrated that increased expression levels of galectin-3 are associated with mortality in acute and chronic HF (20,22), whereas another systematic review indicated that galectin-3 is ineffective for predicting all-cause mortality and cardiovascular mortality, particularly under the influence of certain clinical factors including estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (23).

A prospective cohort study with a 26-month follow-up revealed that galectin-3 expression levels are independent predictors of 26-month mortality in patients with chronic HF, and that a galectin-3 level >21 ng/ml was associated with increased mortality (24). In HF patients with coronary heart disease, serum galectin-3 levels were increased, and were an independent predictor of all-cause mortality and re-hospitalization. Galectin-3 levels were markedly associated with outcomes in HF patients with a preserved ejection fraction (HFpEF) compared with HF patients with a reduced ejection fraction (HFrEF) (25). Galectin-3 is also associated with HF severity and exhibits dynamic changes during mechanical unloading, and predicts survival rates following the use of a left ventricular assist device (LVAD). Furthermore, galectin-3 is associated with the development of cardiac allograft vasculopathy post-heart transplantation (HT). Galectin-3 may also serve as a novel biomarker in patients with HF, during LVAD support, and following HT (26). Using patients hospitalized for HF pooled from three cohorts, Meijers et al (27) demonstrated that the plasma galectin-3 concentration is useful for the prediction of near-term re-hospitalization (27). In patients with HF and functional mitral regurgitation who underwent mitral valve repair, high pre-operative serum galectin-3 was independently associated with the absence of left ventricular (LV) reverse remodeling following mitral valve repair (28). Furthermore, the prognostic value of galectin in patients with HF is not affected by HF therapeutic strategies (29-31) or age (32). However, the prognostic value of galectin-3 in HF may differ among various ethnicities. Using a sub-study of the Atherosclerosis Risk in Communities observational cohort (1,375 white patients and 434 black patients) between 2004 and 2005, galectin-3 was identified to be independently associated with a composite of HF or mortality among white patients; however, not among black patients. Thus, galectin-3 may have limited prognostic utility for predicting HF and mortality in black patients (33).

Changes in galectin-3 over time may be a more sensitive and accurate prognostic biomarker for HF. Galectin-3 expression levels are elevated in a substantial proportion of patients with HF, particularly those with more severe HF and renal dysfunction (34). Galectin-3 expression levels increase over time in these patients and the increase is independently associated with a poorer clinical outcome (34). In the Valsartan Heart Failure Trial over a 4-month follow-up, for every 1 µg/l increase in galectin-3, there was an associated increased risk of mortality, primary morbid event and also hospitalization for HF (2.9, 2.1 and 2.2%, respectively) (34). In the Controlled Rosuvastatin Multinational Trial in Heart Failure (over a 3-month follow-up) and in the Coordinating Study Evaluating Outcomes of Advising and Counseling Failure trial (over a 6-month follow-up), increased galectin-3 expression levels were observed (<17.8 to >17.8 ng/ml). This was associated with a significant increase in hospitalization and mortality.
due to HF, with an increase of >15% corresponding to a 50% increase in relative hazard of adverse events, despite following extensive clinical adjustments including age, sex, diabetes mellitus, LVEF, renal function, medication (e.g. β-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers) and NT-proBNP (35). In patients with LV systolic dysfunction with >10-month follow-up, an increase <20 ng/ml was significantly associated with a lower rate of adverse cardiovascular events and independently predicted fewer adverse cardiovascular events following extensive clinical adjustments. However, HF therapeutic strategies including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and thiazide diuretic exhibited no clear effects on galectin-3 expression levels (29). In patients with stable chronic HF, the change in galectin-3 expression levels over time, including that at 6 months, are improved predictors of cardiovascular events compared with baseline galectin-3 levels (36). In contrast, Miller et al (37) identified that serial galectin-3 monitoring in ambulatory HF patients provided no additional prognostic benefit.

The association of galectin-3 with other cardiac function parameters remains controversial. A previous study demonstrated that in-patients with acute decompensated HF exhibited no significant association between serum galectin-3 expression levels and arterial stiffening markers, whereas increased galectin-3 expression levels were associated with impaired ventricular-arterial coupling, elevated pulmonary artery pressures and severe systolic dysfunction (38). Increased galectin-3 expression levels and arterial pulmonary pressure were identified to be independent risk factors for all-cause mortality and readmission (38). Galectin-3 expression levels demonstrated no difference between patients with HFpEF or HFrEF. However, it was associated with diastolic dysfunction severity and LV stiffness in patients with HFrEF, and associated with poor clinical outcome(s) independent of renal dysfunction and other risk factors in patients with HFpEF (39). Furthermore, for patients with compensated systolic HF undergoing treatment, galectin-3 demonstrated no association with eGFR, LVEF or functional capacity (40). The serum levels of galectin-3 are associated with changes in the LV structure and function, indicating that galectin-3 may be involved in the process of LV remodeling in chronic HF (41). Galectin-3 reflects the inflammatory status and fibrosis, and may be useful for evaluating cardiac and renal function; as such, it may serve as a cardio-renal biomarker. In outpatients with HF, increased serum levels of galectin-3 reflected increased neurohumoral activity and reduced eGFR, however, not myocardial function (42). In another study enrolling a group of outpatients with chronic HF, galectin-3 serum levels were significantly and independently associated with microalbuminuria (43). However, Zhang et al (44) reported that for inpatients with HF, galectin-3 only predicted mortality associated with renal function for patients with an eGFR >60 ml/min/1.73 m². Furthermore, for patients with HFpEF, galectin-3 was associated with renal dysfunction severity, and was not independently associated with the severity of pathophysiologic derangements (45). Another cohort study confirmed that galectin-3 was markedly associated with renal function in outpatients with HF (46). Collectively, these results indicate that the adjustment for renal function may be required when interpreting the significance of galectin-3 expression levels.

The prognostic value of galectin-3 has also been compared with that of other available biomarkers. The Penn Heart Failure study assessed an ambulatory HF cohort, which was comprised of patients with reduced, preserved or recovered LVEF. When this was compared with the established biomarkers for HF [including soluble suppression of tumorigenicity 2 (sST2), troponin I and B-type natriuretic peptide (BNP)], galectin-3 and BNP were revealed to be the most accurate risk discriminators for patients with preserved and recovered LVEF through a 5 year follow-up, respectively (47). In patients with HFpEF, galectin-3 was a significantly more sensitive, but less specific as a biomarker when compared with BNP (48), whereas another study demonstrated the opposite conclusion, that the specificity of galectin-3 for predicting chronic HF was increased compared with that of N-terminal pro-BNP (NT-proBNP; however, its sensitivity was not comparatively increased (49). When patients with HF were stratified using eGFR values and the predictive value of fibroblast growth factor-23, galectin-3 and sST2 was compared, sST2 was the best predictor of mortality in patients with the lowest eGFR values, fibroblast growth factor-23 was the most relevant biomarker for patients with HF and intermediate eGFR values, and galectin-3 was the best biomarker for patients with HF and eGFR values >73 ml/min/1.73 m² (50). However, galectin-3 has decreased prognostic value compared with matrix metalloproteinase-2 regarding clinical outcome prediction in patients with chronic systolic HF (51). In addition, galectin-3 has less prognostic value than sST2 for long-term risk stratification of ambulatory HF patients (52). One study speculated that sST2 may be more useful for monitoring long-term HF and that galectin-3 may be more useful for the diagnosis of HF remodeling (53).

The combination of galectin-3 with BNP provided an improved predictive value in discharged patients with HF following an acute decompensated HF episode compared to BNP alone (54). Galectin-3 alone as a risk predictor was not effective enough to assess sudden or in-hospital mortality, whereas combining galectin-3 and NT-proBNP levels significantly improved discrimination and reclassification when predicting all-cause and cardiovascular-associated mortality (55). The combination of galectin-3 and ST2 may be used to identify high systemic fibrosis in patients with acute HF, thus providing a powerful risk stratification value (56). Therefore, galectin-3 is not recommended for use as a single prognostic biomarker for patients with HF; however, it is recommended in combination with other established biomarkers (23).
Table I. Biomarker characteristics of galectin-3 in different types of disease.

| Author, year | Disease                          | Parameter                           | Biomarker value | Outcome                              | (Refs.) |
|--------------|---------------------------------|-------------------------------------|-----------------|--------------------------------------|---------|
| Medvedeva et al 2016, Yu et al 2015 | Heart failure                  | Baseline serum galectin-3 levels    | Prognostic      | Mortality                            | (24,25) |
| Yu et al 2015, Meijers et al 2014 |                                  |                                     |                 | Rehospitalization                    | (25,27) |
| Anand et al 2013, van der Velde et al 2013 |                                  | Changes of serum galectin-3         | Prognostic      | Mortality and hospitalization         | (34,35) |
| Motiwala et al 2013, Piper et al 2016 |                                  |                                     |                 | Cardiovascular events                | (29,36) |
| Zhang et al 2016, Polat et al 2016 |                                  | Serum galectin-3 levels             | Diagnostic      | NA                                   | (57,58) |
| Zhang et al 2016 |                                  | Salivary galectin-3                | Diagnostic      | NA                                   | (57)    |
| Maiolino et al 2015, Tunon et al 2014 | Coronary heart disease          | Baseline serum galectin-3 levels    | Prognostic      | Cardiovascular events                | (62,63) |
| Jansen et al 2016 |                                  |                                     |                 |                                       | (64)    |
| Takemoto et al 2016, Clementy et al 2016, Wu et al 2015 | Atrial fibrillation             | Baseline serum galectin-3 levels    | Prognostic      | Atrial tachyarrhythmia recurrences   | (79,81,82) |
| Ozkan et al 2015, Hogas et al 2016 |                                  | Hemodialysis                        | Baseline serum galectin-3 levels | Prognostic | Mortality                            | (110,111) |
| Kaneko et al 2013 |                                  | Renal cell carcinoma                | Serum galectin-3 and galectin-1 levels | Diagnostic | NA                                   | (114)    |
| Manivannan et al 2012, Mataraci et al 2012, Matesa-Anic et al 2012, Sumana et al 2015, Al-Sharaky et al 2016, Yilmaz et al 2015 | Thyroid carcinoma                | Tissue galectin-3 expression        | Diagnostic      | NA                                   | (119-122,125,126) |

*With prognostic value; †without prognostic value.
Galectin-3 may also be used for the diagnosis of HF. In a previous study, the areas under the receiver operating characteristic curve for serum and salivary galectin-3 were 0.86 and 0.73, respectively (57). In patients with HFpEF, the area under the curve for serum galectin-3 was 0.98 (58). These results indicated the potential utility of using galectin-3 to diagnose HF.

Coronary heart disease (CHD) and myocardial infarction (MI). In patients with aortic valve stenosis, galectin-3 expression levels in serum and the myocardium were positively associated with levels of fibrosis and relative wall thickness, which are crucial indicators of geometric remodeling (59). Furthermore, galectin-3 in valvular interstitial cells obtained from patient’s aortic stenosis induced the expression of inflammatory, fibrotic and osteogenic markers. In addition, its inhibitor, modified citrus pectin, decreased the expression levels of inflammatory, fibrotic and osteogenic markers in valvular interstitial cells undergoing osteoblastic differentiation, indicating its potential function in calcification in aortic stenosis (60). However, a prospective study which enrolled patients with at least mild degenerative aortic stenosis from two ongoing cohort studies demonstrated that galectin-3 was not associated with aortic stenosis severity or functional status, and did not provide prognostic information on the occurrence of aortic stenosis-associated events (61).

In a prospective cohort study with long-term follow-up (median, 7.2 years) in patients with CHD, galectin-3 presented as a strong independent predictor of cardiovascular mortality (62). In patients with chronic CHD, increased serum galectin-3 levels were associated with a greater incidence of cardiovascular events (63). In contrast, another large cohort study with a 13-year follow-up of patients with CHD, galectin-3 expression level increased despite HT, and was associated with a 1.5-fold increased risk of cardiovascular events (64). Galectin-3 was not able to independently predict recurrent cardiovascular events (65). In patients with coronary artery disease, serum galectin-3 levels exhibited a significantly positive association with coronary artery disease severity, as determined by the Gensini score and number of diseased vessels (65), and increased serum levels of galectin-3 reflected the increased degree of myocardial fibrosis (66). Contrastingly, in patients with acute coronary syndrome, serum galectin-3 levels demonstrated a significantly positive association with the Gensini score; however, not with the number of diseased vessels (67). In addition, acute coronary syndrome patients with higher galectin-3 expression levels exhibited a decreased LVEF and eGFR (68).

In patients with a first anterior ST-elevated myocardial infarction (STEMI) and left anterior descending artery occlusion treated by primary percutaneous coronary intervention (pPCI), increased galectin-3 serum levels were measured during hospitalization and were associated with an increased risk of LV remodeling (69). Furthermore, elevated galectin-3 expression levels were associated with a higher rate of new-onset atrial fibrillation (AF) and diuretic treatment during hospitalization, and were the most effective independent predictor of the combined 30-day major adverse clinical outcome in patients with first MI without prior HF treated with pPCI (70,71). Galectin-3 levels were also associated with reinfarction following initial MI (72). Galectin-3 measured acutely following STEMI was demonstrated as an independent predictor of increased extracellular volume during a 6-month follow-up, which may be useful for long-term risk stratification (73), and may be used to predict LVEF and infarction size after 4 months when measured immediately following a MI (74). In addition, serum galectin-3 levels varied significantly following a STEMI over a short time period and were associated with the timing of reperfusion (75). In acute MI, galectin-3 expression levels were positively and significantly associated with certain inflammatory factors (76), whereas another study demonstrated that galectin-3 expression levels did not change during acute MI and had no association between galectin-3 levels and acute ischemic myocardial injury (77). In acute MI, galectin-3 was positively and significantly associated with certain biomarkers including matrix metalloproteinase 3, monocyte chemoattractant protein-1, and interleukin (IL)-8 involved in extracellular matrix turnover, but not with LV remodeling (78). Furthermore, galectin-3 was positively associated with MI size and LV remodeling in patients with a history of complicated MI (79).

Other types of cardiac disease. Galectin-3 expression levels were increased in patients with AF, particularly in persistent AF (79,80). Furthermore, galectin-3 expression independently predicted atrial tachyarrhythmia recurrences following a single ablation procedure (79,81,82). In addition, galectin-3 was independently associated with new-onset AF (83), with atrial remodeling (84) and with left atrial volume index in AF patients with preserved LV function (80). However, the rhythm outcome of catheter ablation cannot be predicted using galectin-3 levels (85).

In patients with hypertension, galectin-3 was independently associated with LV remodeling and, therefore, may be a valuable biomarker for the detection of early cardiac remodeling in hypertension (86). In addition, it was associated with ambulatory microvolt T-wave alternans positivity, decreased eGFR and increased LV myocardial index in hypertensive patients (87). Increased galectin-3 expression levels were observed in patients with pulmonary arterial hypertension (88). Increased galectin-3 was associated with multiple indices of right ventricle function and morphology (88), and was predictive of impaired right ventricle function (89).

In patients with hypertrophic cardiomyopathy, galectin-3 expression levels were increased and associated with the increased degree of LV hypertrophy; however, it was not associated with decreased myocardial LV diastolic and systolic functions (90). Furthermore, galectin-3 was associated with late gadolinium enhancement-assessed myocardial replacement fibrosis in patients with non-ischemic dilated cardiomyopathy (91).

Galectin-3 may serve as a biomarker for post-HT outcomes. Galectin-3 analyzed 10 days following HT displayed an association with heart function assessed 1 year after HT (92). Furthermore, galectin-3 fluctuated in patients followed up for 12 months after HT, and a novel process was indicated when galectin-3 increased by double or decreased by one-half compared to the baseline level (93). Contrastingly, Grupper et al (94) reported that although the galectin-3 expression level increased despite HT, and was associated with
renal dysfunction, it was not associated with the presence of myocyte hypertrophy and interstitial fibrosis post HT (94).

Patients exhibiting peripheral artery disease also demonstrated increased galectin-3 levels, and galectin-3 was positively associated with homeostatic model assessment, but not arterial elasticity and microalbuminuria following adjustment for age and sex (95). A prospective observational study indicated that elevated plasma galectin-3 levels were markedly associated with inflammation, severity and poor prognosis following intracerebral hemorrhage (96). In adults with single-ventricle Fontan circulation, elevated galectin-3 was associated with an increased risk of non-elective cardiovascular hospitalization or mortality (97). Contrastingly, a low galectin-3 intra-plaque concentration appears to be associated with clinically and ultrasonically defined unstable human carotid plaques in patients with high-grade carotid stenosis (98).

An increased plasma galectin-3 level was associated with increased myocardial fibrosis in patients with aldosterone-producing adenoma (99). In addition, increased plasma levels of galectin-3 facilitate with predicting the occurrence of postoperative strokes among female patients who undergo carotid endarterectomy (100). Galectin-3 expression levels were also associated with the severity and a poor prognosis following aneurysmal subarachnoid hemorrhage (101). However, in the general population, galectin-3 did not predict incident cardiometabolic disease following adjustment for cardiometabolic risk factors (102).

3. Galectin-3 and renal disease

Renal failure and associated complications. In a rat model of ischemia/reperfusion and folic acid-induced acute renal failure (ARF), galectin-3 mRNA expression levels began to increase 2 h after injury, and the increased levels continued until 28 days after injury in ischemic ARF and 7 days after injury in toxic ARF. Furthermore, in ischemic ARF, the level of galectin-3 mRNA expression was significantly negatively associated with serum reciprocal creatinine levels at 48 h of galectin-3 mRNA expression was significantly negatively associated with increased mRNA expression levels of galectin-1 and -3 in clear cell RCC, indicating that galectins may be involved in the pathogenesis of the higher prevalence of RCC in men (115). A marked overexpression of galectin-3 was predominantly identified in renal tumors with oncocytic features, including oncocytomas and chromophobe RCC with positive immunohistochemical rates of 100 and 89%, respectively, whereas significantly decreased expression levels of galectin-3 were observed in clear cell and papillary RCCs (113). Furthermore, the combined use of galectin-1 and -3 for RCC
diagnosis demonstrated specificity and sensitivity of 98 and 47%, respectively (114). These results indicated the potential role of galectin-3 in the diagnosis of different types of RCC (Table I).

4. Galectin-3 and cancer

Thyroid carcinoma. Differentiating malignant lesions from benign thyroid lesions is clinically challenging. Even the most accurate method, thyroid fine needle aspiration biopsy, has only 70-90% accuracy (118). Thus, as a pro-angiogenic marker, the value of galectin-3 in the diagnosis of thyroid carcinoma has been widely investigated (Table I). The latest meta-analysis indicated that galectin-3 may be a potentially useful immunomarker to distinguish between patients with papillary thyroid carcinoma (PTC) and patients without PTC. In addition, PTC patients with positive expression of galectin-3 were prone to lymph node metastasis (118). However, there are controversial results regarding other types of thyroid carcinoma.

Previous studies support the potential diagnostic value of galectin-3 for malignant lesions. Manivannan et al (119) demonstrated that galectin-3 expression levels in tumor tissues differentiate benign from malignant follicular neoplasms. Focal and diffuse positivity for galectin-3 was associated with malignant thyroid follicular neoplasms (119). Mataraci et al (120) also identified that the percentage and intensity of staining for galectin-3 were increased in malignant lesions, particularly in papillary carcinomas (120). Galectin expression levels were significantly increased in malignant thyroid neoplasms when compared with benign neoplasms. However, no significant differences were identified when comparing galectin-3 expression levels in PTC and other malignant lesions. Previous studies have demonstrated that there was no marked staining intensity for intracytoplasmatic or intranuclear expression of galectin-3 in benign thyroid neoplasms. Furthermore, there was a lack of weak intensity for intracytoplasmatic or intranuclear expression of galectin-3 in malignant neoplasms, therefore, diffuse and strong staining for galectin-3 differentiates malignant from benign thyroid neoplasms. Overexpression of galectin-3 protein was observed in papillary thyroid carcinoma with lymph node metastases (124). A previous study compared glypican-3 (a member of the glypican family of heparan-sulfate proteoglycans bound to the plasma membrane) with galectin-3 and demonstrated that galectin-3 was more sensitive in diagnosing thyroid carcinoma; however, it was less specific in discriminating follicular-patterned neoplasm (125). Besides tissue expression, the preoperative serum galectin-3 level had diagnostic value, as it was significantly higher in the cancer patients than in the control subjects (126).

Galectin-3 is also used in combination with other biomarkers for a differential diagnosis of thyroid lesions. The most commonly combined biomarkers are Hector Battifora mesothelial epitope-1 (HBME-1) and cytokeratin-19 (127-130). Galectin-3 and HBME-1 may be used as single discriminators between follicular thyroid adenoma and carcinoma. Significant differences in galectin-3 and HBME-1 were identified between benign and malignant lesions, and also between the subgroups of benign and malignant lesions (127-130). Galectin-3 and HBME-1 have an excellent sensitivity and specificity for malignant thyroid lesions (100 and 89.1%, respectively) (129). Despite core needle biopsies leading to the diagnosis of the majority of thyroid nodules, the accuracy is increased by also observing the galectin-3, cytokeratin-19 and HBME-1 panels, indicating their additional diagnostic value when combined with routine histology (127-130). It was also reported that galectin 3, cluster of differentiation (CD)44 and, to an extent, HBME-1, are useful immunocytochemical parameters with the potential to support the fine needle aspiration cytology diagnosis of PTC, particularly in situations where the differential diagnoses is complicated (131). The levels of parafibromin and galectin-3 expression were significantly increased among patients with parathyroid adenoma, atypical parathyroid adenomas and parathyroid carcinoma, whereas HBME-1 expression levels were not (132). The level of parafibromin expression was increased, whereas galectin-3 expression was decreased in arathyroid adenoma (132). Parafibromin expression, galectin-3 negativity, and a Ki-67 proliferation index <1% were identified to be beneficial in the differential diagnosis of parathyroid tumors (132). Another study reported that the loss of parafibromin and overexpression of galectin-3 and Ki-67 may assist in distinguishing parathyroid carcinoma from other types of parathyroid tumor (133). The combination of two or three of these markers may produce improved sensitivity and/or specificity for the diagnosis of parathyroid carcinoma (133). Galectin-3 and Bcl-2 exhibited a similar trend of downregulation from high levels in PTC to low levels in anaplastic thyroid carcinoma. During thyroid tumor progression from PTC to anaplastic thyroid carcinoma, down-regulation of galectin-3 and Bcl-2 (antiapoptotic molecules) and a stepwise increase in survivin (inhibitor of apoptosis) were observed (134).

Contrastingly, certain studies indicated that galectin-3 is not a potential diagnostic or prognostic biomarker (135-138). Studies demonstrated that galectin-3 expression levels in tumor tissues were not significantly associated with age, sex, extrathyroidal extension, lymph node metastasis, or total metastasis, age, completeness of resection, invasion or size score category and cannot be used for prognostic prediction (135). In thyroid tumors of uncertain malignant potential, cytokeratin-19, galectin-3, HBME-1, and CD56 stained negatively in the majority of cases (90.3, 83.9, 87.1 and 61%, respectively), and no statistically significant differences were observed when compared with the immunoprofile of benign thyroid lesions (136). In another study assessing the efficacy of cytokeratin 19, thyroperoxidase, HBME-1 and galectin-3 in the evaluation of the aggressiveness of PTC, increased levels of cytokeratin 19 expression and negative thyroperoxidase expression indicated the total tumor diameter of PTC; however, the expression levels of cytokeratin 19, thyroperoxidase, HBME-1, and galectin-3 did not contribute to the identification of PTCs with other potentially aggressive behaviors (137). In papillary microcarcinoma, the level of galectin-3 expression exhibited no significant association with prognostic factors, including extrathyroidal extension and lymph node metastasis (138).
Hepatocellular carcinoma (HCC). Galectin-3 promotes tumor progression in HCC. In mice bearing HCC, the galectin-3 expression level in tumor tissue was significantly increased, while serum galectin-3 levels also demonstrated obvious changes (139). In an N-diethylNitrosamine-induced HCC mouse model, galectin-3 knockout mice developed a significantly smaller tumor burden with a less invasive phenotype compared with the wild-type animals. Galectin-3 was upregulated in the wild-type HCC tumor tissue; however, not in the surrounding parenchyma. In vitro studies demonstrated that the migration of hepatoma cells was significantly decreased and the reorganization of the actin cytoskeleton, RhoA GTPase activity and phosphorylation of myosin light chain 2 were decreased in the galectin-3 small interfering RNA-transfected cells. Furthermore, in vitro and in vivo evidence demonstrated that galectin-3 deficiency reduced hepatoma cell proliferation and increased apoptosis among these cells. These results indicated that galectin-3 promotes hepatoma cell motility and invasion via an autocrine signaling pathway (140). Serum galectin-3 levels were decreased in chronic hepatitis B or C patients when compared with patients with HCC and cirrhosis; however, there were no significant differences identified between patients with HCC and patients with cirrhosis (141). Another study confirmed that there was no difference in serum galectin-3 levels in HCC and cirrhotic patients (142). HCC patients with metastatic spread and poor prognosis suffering from portal vein invasion exhibited elevated serum galectin-3 levels (142). Expression levels of galectin-3 in HCC tissues were significantly increased and were associated with a poor prognosis. Furthermore, galectin-3 expression levels in tumor cells stimulated angiogenesis (143). Collectively, these results indicate that galectin-3 may be used for prognosis, but not for the diagnosis of patients with HCC.

Prostate cancer. At present, results regarding the serum levels and tissue expression of galectin-3 in patients with prostate cancer are controversial. In patients with metastatic prostate cancer, serum galectin-3 levels were uniformly higher compared with those in control subjects without cancer (144). Furthermore, serum galectin-3 levels were positively associated with prostate specific antigen in prostate cancer patients, particularly at early clinical time course (145). Galectin-3 expression levels in prostate tissue were increased in benign prostatic hyperplasia compared with normal tissue samples and markedly lower in adenocarcinoma (146). Galectin-3 demonstrated nuclear and cytoplasmic localization in benign, adjacent-benign and tumor tissues, with a decreasing gradient of galectin-3 expression levels observed in benign, adjacent-benign and tumor tissue samples (147).

Pancreatic carcinoma. Tissue expression and serum levels of galectin-3 were significantly higher in pancreatic carcinoma tissues or patients with pancreatic carcinoma when compared with the adjacent non-tumorous tissues or in benign pancreatic diseases and healthy individuals (148). Higher galectin-3 expression levels in tissues were associated with poor differentiation tissues (148). Serum galectin-3 was not associated with carcinoma embryonic antigen and CA19-9; however, a combination of these three markers may increase the diagnostic sensitivity of pancreatic carcinoma diagnosis to 97.5% (148). Furthermore, galectin-3 was differentially expressed in different pancreatic carcinoma tissues (149). Furthermore, there was an increased expression in pancreatic ductal adenocarcinoma; however, not in pancreatic neuroendocrine neoplasms and gastrointestinal stromal tumors. Thus, galectin-3 may be used to help diagnose pancreatic ductal adenocarcinoma and rule out pancreatic neuroendocrine neoplasms and gastrointestinal stromal tumors (149).

Colorectal cancer. The serum level of galectin-3 was increased 11.3-fold in patients with colorectal cancer and markedly increased 31-fold in those with metastases (150). Simultaneous determination of serum galectin-3 and -4 levels demonstrated an increased specificity and sensitivity in distinguishing patients with colorectal cancer without metastases from those with liver metastases. Furthermore, increased serum galectin-3/-4 expression levels at the time of primary tumor removal in patients without clinically detectable metastases were associated with poorer survival rates over the next 10 years (151). Increased serum galectin-3 expression levels were observed in patients with colon cancer when compared in patients with rectal cancer (152). No association was identified between tissue galectin-3 expression levels and clinicopathological parameters of patients with colorectal cancer, whereas the level of tissue galectin-3 expression was positively associated with serum IL-17 and IL-23. Serum galectin-3 levels were significantly associated with IL-17, but not IL-23 in patients with colorectal cancer (153). Shimura et al (152) also confirmed the serum galectin-3 levels was associated with IL-17 production. Furthermore, it was also inversely associated with the production of IL-10 and IL-12 (152). These results indicated that galectin-3 may be a key factor in the regulation of tumor-associated inflammatory processes.

Breast cancer. Expression levels of galectin-3 protein were significantly greater in the breast tumor tissues compared with the paracancerous tissue, and galectin-3 was markedly expressed in triple-negative breast cancers when compared with other types of breast cancer (154,155). Furthermore, the expression levels of galectin-3 were not identified as an independent prognostic factor for breast cancer, but were associated with chemotherapeutic resistance (154). In addition, the serum galectin-3 level was significantly increased in breast cancer patients compared with healthy control subjects (150). However, two previous studies demonstrated that low galectin-3 expression levels in breast cancer were significantly associated with increased tumor vascular invasion, and reduced disease-free survival and long-term overall survival (156,157). Furthermore, in vitro breast cancer stem cell models demonstrated that galectin-3 knockdown led to epithelial-mesenchymal transition, increased sphere-formation ability, drug-resistance and increased aldefluor activity. In addition, in vivo orthotopic mouse models demonstrated that galectin-3-negative breast cancer stem cells were associated with enhanced tumorigenicity. These results indicated that loss of galectin-3 may be associated with epithelial-mesenchymal transition and cancer stemness-associated traits, and therefore, may predict poor response to chemotherapy and poor prognosis (157).
Bladder cancer. The serum and tissue expression levels of galectin-3 were statistically increased in patients with bladder cancer compared with control and cystitis groups. Serum galectin-3 levels were increased in patients with transitional cell carcinoma compared with squamous cell carcinoma. Patients with high-grade transitional cell carcinoma had a significantly increased serum galectin level compared with those with low-grade tumors, as did those with muscle-invasive transitional cell carcinoma compared with papillary non-invasive tumors (158,159). These results indicated that galectin-3 may be a potential diagnostic biomarker for bladder cancer.

Gastric cancer. Serum levels of galectin-3 in patients with gastric cancer were significantly increased compared with those in benign disease patients and healthy control subjects, and the serum galectin-3 level was associated with lymph node metastasis and distant metastasis (160). Tissue galectin-3 expression was reduced by 1.5-fold in 50% of gastric tumors. The reduced galectin-3 expression level was associated with the presence of distant metastasis, and with a higher invasive phenotype in vitro (161). In contrast, it was previously reported that baseline serum galectin-3 levels exhibited no significant difference between patients with gastric cancer and healthy control subjects. Serum galectin-3 levels were not associated with the stage of disease or chemotherapy responsiveness (162). However, these studies confirmed that the galectin-3 expression level had no association with overall survival rates, and was not a reliable biomarker for determining prognosis in gastric adenocarcinoma (160,162,165).

Lymphoma. Serum galectin-3 levels were significantly higher in patients with non-acute promyelocytic leukemia compared with the control group subjects. Patients with higher galectin-3 expression levels had lower complete remission rates and a significantly shorter overall survival. An increased galectin-3 expression level was an independent poor prognostic marker (164). Furthermore, serum galectin-3 levels in patients with non-Hodgkin's lymphoma were associated with cardiovascular events and were significantly increased in patients with cardiovascular events compared with patients without a cardiovascular event. Overall, increased serum galectin was associated with increased 12-month cumulative cardiovascular events (165).

Other types of cancer. High expression levels of galectin-3 in endometrial tumor tissues were independently associated with tumor depth and histological grade, and were associated with shorter survival rates (166). The serum and tissue expression levels of galectin-3 were significantly increased in patients with osteosarcoma compared with control subjects. Increased galectin-3 expression levels in serum or tumors was associated with the Enneking stage of cancer (167). Furthermore, an increased tumor expression level was associated with the occurrence of metastasis (167). In oral squamous cell carcinoma, serum and tissue expression levels of galectin-3 were significantly increased compared with those in control subjects. Patients with an increased tumor load exhibited an increased expression of galectin-3 compared with those with a decreased tumor load. Furthermore, exogenous galectin-1 treatment significantly increased survival, proliferation and angiogenesis in oral squamous cell carcinoma cell lines (168).

Gastric cancer. Serum levels of galectin-3 in patients with gastric cancer were significantly increased compared with those in benign disease patients and healthy control subjects, and the serum galectin-3 level was associated with lymph node metastasis and distant metastasis (160). Tissue galectin-3 expression was reduced by 1.5-fold in 50% of gastric tumors. The reduced galectin-3 expression level was associated with the presence of distant metastasis, and with a higher invasive phenotype in vitro (161). In contrast, it was previously reported that baseline serum galectin-3 levels exhibited no significant difference between patients with gastric cancer and healthy control subjects. Serum galectin-3 levels were not associated with the stage of disease or chemotherapy responsiveness (162). However, these studies confirmed that the galectin-3 expression level had no association with overall survival rates, and was not a reliable biomarker for determining prognosis in gastric adenocarcinoma (160,162,165).

Results regarding abnormal expression levels of galectin-3 in cancer have been summarized in Table II. Collectively, these studies reveal that galectin-3 is expressed abnormally in many types of cancer, which indicates that galectin-3 is not a tumor-specific biomarker. Thus, galectin-3 will be effective when applied in combination with other specific biomarkers.

5. Galectin-3 as a therapeutic target

As galectin-3 has been demonstrated to perform numerous functions in the pathogenesis of diseases outlined previously, and may serve as a therapeutic target for these diseases, its potential clinical applications have been evaluated using cell and animal models (Table III). RN1, a polysaccharide that binds to galectin-3 and suppresses its expression, significantly inhibited growth of pancreatic ductal adenocarcinoma cells in vitro, in vivo and in patient-derived xenografts (171). Galectin-3 targeted N-(2-hydroxypropyl) methacrylamide copolymer-(G3-C12)-5-fluorouracil conjugates significantly improved the anti-tumor activity of fluorouracil in nude mice bearing PC-3, a prostate tumor xenograft (172). TFID100, a glycopeptide from cod binds galectin-3 with picomolar affinity and blocks galectin-3-mediated angiogenesis, tumor-endothelial cell interactions and metastasis of prostate cancer cells in mice (173). Galectin-3C, a truncated, dominant negative form of galectin-3, hypothesized to act by blocking endogenous galectin-3, significantly reduced the growth, motility, invasion, and angiogenic potential of cultured ovarian cancer cell lines and primary cells established from ovarian cancer patients (174). Modified citrus pectin, a galectin inhibitor, blocked aldosterone-induced cardiac and renal fibrosis, and improved cardiac function in a mouse model (175). In addition, modified citrus pectin prevented isoproterenol-induced LV dysfunction and fibrosis in mice with HF and cardiac-specific hyperaldosteronism (176). N-acetyllactosamine, a galectin-3 inhibitor, reduced proteinuria, improved renal function and decreased renal damage in mice with hypertensive nephropathy and HF (177). Galectin-3-antagonists and a selective galactose-coumarin-derived galectin-3 inhibitor attenuated bleomycin-induced pulmonary fibrosis in mouse models (179,180). GR-MD-02, a complex carbohydrate-based
Table II. Abnormal expression of galectin-3 in cancer types.

| Author, year                        | Type of cancer          | Location       | Expression | (Refs.)       |
|-------------------------------------|-------------------------|----------------|------------|---------------|
| Bing et al 2013, Kaneko et al 2013, Klot et al 2014, Straube et al 2011, Sakaki et al 2010 | Renal cell carcinoma    | Tumor tissue   | Upregulated | (113-117)     |
| Kaneko et al 2013                   |                         |                |            |               |
| Manivannan et al 2012, Mataraci et al 2012, Matesa-Anic et al 2012, Sumana et al 2015, Papale et al 2013, Salajegheh et al 2014, Al-Sharaky et al 2016 | Thyroid carcinoma      | Tumor tissue   | Upregulated | (119-125)     |
| Kaneko et al 2013                   |                         | Serum          | Upregulated | (114)         |
| Straube et al 2011, Sakaki et al 2013 |                         | Serum          | Upregulated | (114)         |
| Manivannan et al 2012, Mataraci et al 2012, Matesa-Anic et al 2012, Sumana et al 2015, Papale et al 2013, Salajegheh et al 2014, Al-Sharaky et al 2016 | Thyroid carcinoma      | Tumor tissue   | Upregulated | (119-125)     |
| Manivannan et al 2012, Mataraci et al 2012, Matesa-Anic et al 2012, Sumana et al 2015, Papale et al 2013, Salajegheh et al 2014, Al-Sharaky et al 2016 | Thyroid carcinoma      | Tumor tissue   | Upregulated | (119-125)     |
| Yilmaz et al 2015                   |                         | Serum          | Upregulated | (126)         |
| Ulu et al 2015, Eisa et al 2015, Jiang et al 2014 | Hepatocellular carcinoma | Serum         | Upregulated | (141-143)     |
| Balan et al 2013, Nakajima et al 2016 | Prostate cancer        | Serum          | Upregulated | (144,145)     |
| Araujo-Filho et al 2013, Knapp et al 2013 |                         | Tumor tissue   | Downregulated | (146,147)     |
| Xie et al 2012, Jiang et al 2014    |                         | Tumor tissue   | Upregulated | (148,149)     |
| Barrow et al 2011, Barrow et al 2013, Shimura et al 2016 | Colorectal cancer | Serum          | Upregulated | (150-152)     |
| Zhang et al 2014, Koo et al 2011    |                         | Breast cancer  | Tumor tissue | Upregulated   | (154,155)     |
| Barrow et al 2011                   |                         | Serum          | Upregulated | (150)         |
| Yamaki et al 2011, Ilmer et al 2016 |                         | Tumor tissue   | Downregulated | (156,157)     |
| El Gendy et al 2014, Gendy et al 2014 | Bladder cancer         | Serum and tumor tissue | Upregulated | (158,159)     |
| Cheng et al 2015                    |                         | Gastric cancer | Serum       | Upregulated   | (160)         |
| Leal et al 2015                     |                         | Serum          | Downregulated | (161)         |
| Tas et al 2016                      |                         | Serum          | No change   | (162)         |
| Gao et al 2016, Samura et al 2015   | Lymphoma                | Serum          | Upregulated | (164,165)     |
Table III. Galectin-3 as a therapeutic target.

| Author, year        | Substance | Characteristics                                                                 | Disease(s)                | Model(s)                              | (Refs.) |
|---------------------|-----------|---------------------------------------------------------------------------------|---------------------------|---------------------------------------|---------|
| Zhang et al 2016    | RN1       | Polysaccharide purified from the flower of *Panax notoginseng* that binds galectin-3 and suppresses its expression | Pancreatic cancer         | Cell animal Patient-derived xenografts | (171)   |
| Yang et al 2012     | G3-C12    | Peptide that specifically binds to the carbohydrate-recognition domain of galectin-3 | Prostate cancer           | Animal                                | (172)   |
| Guha et al 2013     | TFD100    | Glycopeptide from cod that binds galectin-3 with picomolar affinity and blocks its functions | Prostate cancer           | Animal                                | (173)   |
| Mirandola et al 2014| Galectin-3C | Truncated, dominant negative form of galectin-3 that blocks endogenous galectin-3 | Ovarian cancer            | Cell                                  | (174)   |
| Calvier et al 2015, Vergaro et al 2016, Martinze-Martinez et al 2016, Mackinnon et al 2013 | Modified citrus pectin | Complex water-soluble indigestible polysaccharide, a galectin-3 inhibitor | Hyperaldosteronism Atherosclerosis Obesity | Animal | (175-178) |
| Delaine et al 2016; Rajput et al 2016 | Thiodi-galactosides | Galectin-3 antagonist | Pulmonary fibrosis | Animal | (179,180) |
| Traber et al 2013, Harrison et al 2016 | GR-MD-02 | Complex carbohydrate drug that binds galectin-3 | Non-alcoholic steatohepatitis | Animal human | (181,182) |
drug that binds to galectin-3, improved liver histology with significant reductions in non-alcoholic steatohepatitis (NASH) activity and collagen deposition, and reduced fibrosis in NASH mice with fibrosis (181). Furthermore, GR-MD-02 has been evaluated in a phase I clinical trial in participants with NASH and advanced fibrosis to determine its safety, pharmacokinetics and exploratory pharmacodynamic markers. GR-MD-02 doses were in the upper range (8 mg/kg) of the targeted therapeutic dose determined from pre-clinical data, and were safe and well tolerated with evidence of a pharmacodynamic effect, which therefore provided support for a phase II clinical trial (182).

6. Conclusion

Galectin-3 is a multifunctional protein involved in various types of disease. Its prognostic value in predicting the outcomes of HF and its diagnostic value in thyroid carcinoma diagnosis have been extensively investigated, and indicate its potential application for HF prognosis and thyroid carcinoma diagnosis (Table I). The development of detection methods of galectin-3 is required to improve the sensitivity, accuracy and consensus between different laboratories, and to provide supports for its clinical utility. In addition, normal reference ranges need to be established.

The functions of galectin-3 in fibrosis and immunity have also been extensively investigated, indicating its possible therapeutic utility in certain types of fibrotic disease and infection. In all cases, fibrotic disease progress to severe disease, including HF, renal failure and cirrhosis. Galectin-3 may represent a therapeutic approach to delay the progression of these diseases. Further animal studies and clinical trials are required to develop novel drugs targeting galectin-3.

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