Galectin-3 as Biomarker

Subjects: Biology

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Galectin-3, predominantly located in the cytoplasm and expressed on the cell surface, is a β-galactoside-binding lectin which is important in numerous biological activities in various organs, including cell proliferation, apoptotic regulation, inflammation, fibrosis, and host defense. Galectin-3 is often secreted into biological fluids, like serum and urine, thus used as a biomarker. It is also released from injured cells and inflammatory cells under various pathological conditions. Galectin-3 plays an important role as a diagnostic or prognostic biomarker for certain types of heart disease, kidney disease, viral infection, autoimmune disease, neurodegenerative disorders, and tumor formation. In particular, galectin-3 is extremely useful for detecting many of these diseases in their early stages.

galectin-3 biomarker diagnostic prognostic early stage tumor animal model

1. Introduction

Galectins are a family of widely expressed β-galactoside-binding lectins in modulating “cell-to-cell” and “cell-to-matrix” interactions in all organisms [1][2][3]. Mammalian galectins have either one or two highly conserved carbohydrate recognition domains (CRDs), recognizing β-galactoside residues, to form complexes that crosslink glycosylated ligands [4][5][6].

Galectins have been classified into three subgroups according to their CRD number and function (Figure 1): (1) Proto-type galectins (galectin-1, -2, -5, -7, -10, -11, -13, -14, and -15), containing a single CRD that form non-covalent homodimers, (2) tandem-repeat galectins (galectin-4, -6, -8, -9, and -12), carrying two CRD motifs connected by a peptide linker, and (3) chimera-type galectin (galectin-3), which are characterized by having a single CRD and an amino-terminal polypeptide tail region [2][5][6]. All members of galectin family were numbered consecutively by order of discovery (Figure 1). Galectins are ubiquitously present in vertebrates, invertebrates, and also protists [1].

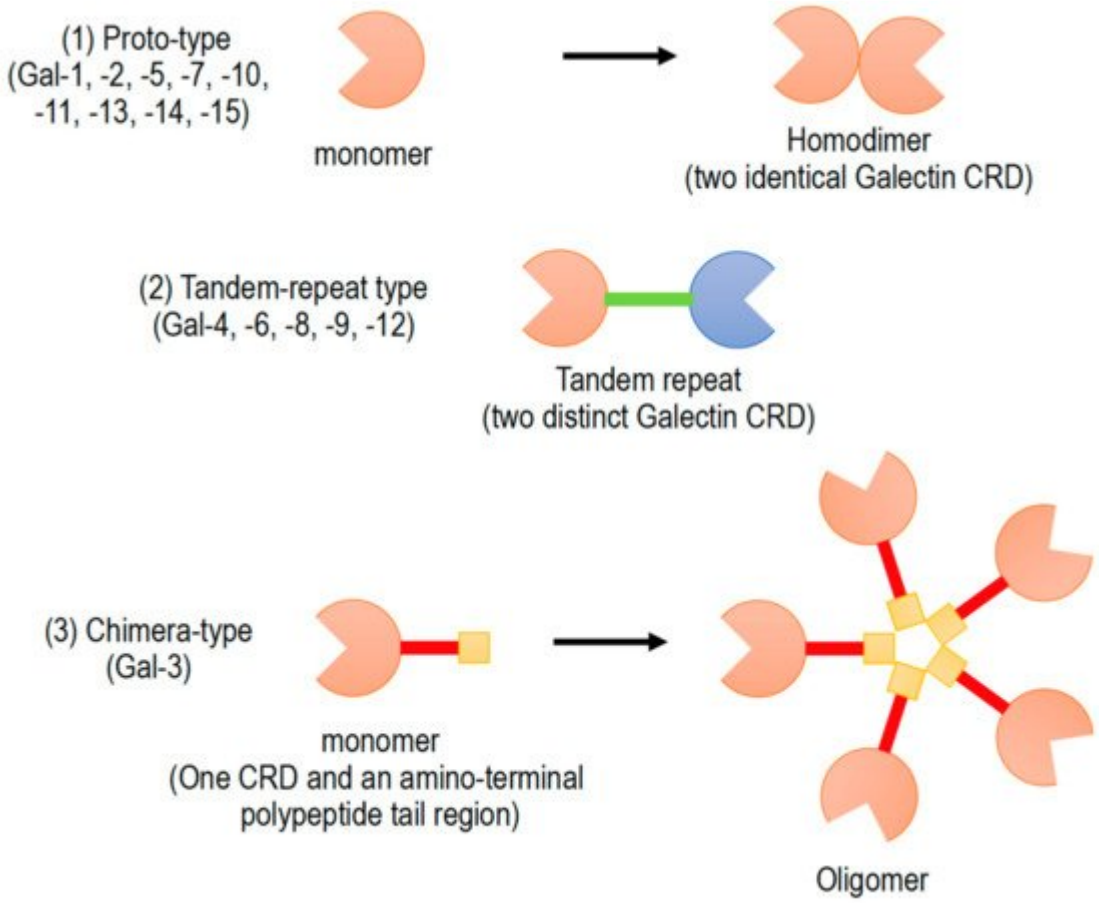

Figure 1. Schematic diagram of galectin family members. Galectin members are divided into three types based on the organization of galectin carbohydrate recognition domain (CRD).

Galectins play important roles in cell-to-cell and cell-to-matrix interactions by binding to endogenous glycans. Galectin signaling can regulate cellular functions at the cell surface. Biological functions of galectins, which are not yet fully understood, include roles in development, tissue regeneration, regulation of immune cell activities, and other important cellular functions [1][2].

Galectins are important regulators of inflammatory responses and immune system. In fact, galectins are expressed in many inflammatory cells, such as macrophages [7]. Depending on the inflammatory environment, galectins promote pro-inflammatory or anti-inflammatory responses [2][5][6]. Recently, the galectin-mediated specific molecular recognition of glycans on the cell surface have revealed their roles as innate immune functions against potential pathogens and parasites. As a part of the innate immune system for microbial recognition/effector functions, galectins bind to exogenously exposed glycans on the surface of viruses, bacteria, fungi, and parasites [3].

2. Clinical Significance and Applications of Galectine-3 (Gal-3)

Gal-3, approximately 30 kDa chimera-type galectin, is expressed in the nucleus, cytoplasm, mitochondrion, cell surface, and extracellular space. Gal-3, to an equal or greater extent than other galectins, plays an important role in cell-to-cell or cell-to-matrix interactions, cell growth and differentiation, macrophage activation, antimicrobial activity, angiogenesis, and apoptosis [8]. Extracellular and intracellular activities of Gal-3 are shown in Figure 2, with references detailed in the caption.

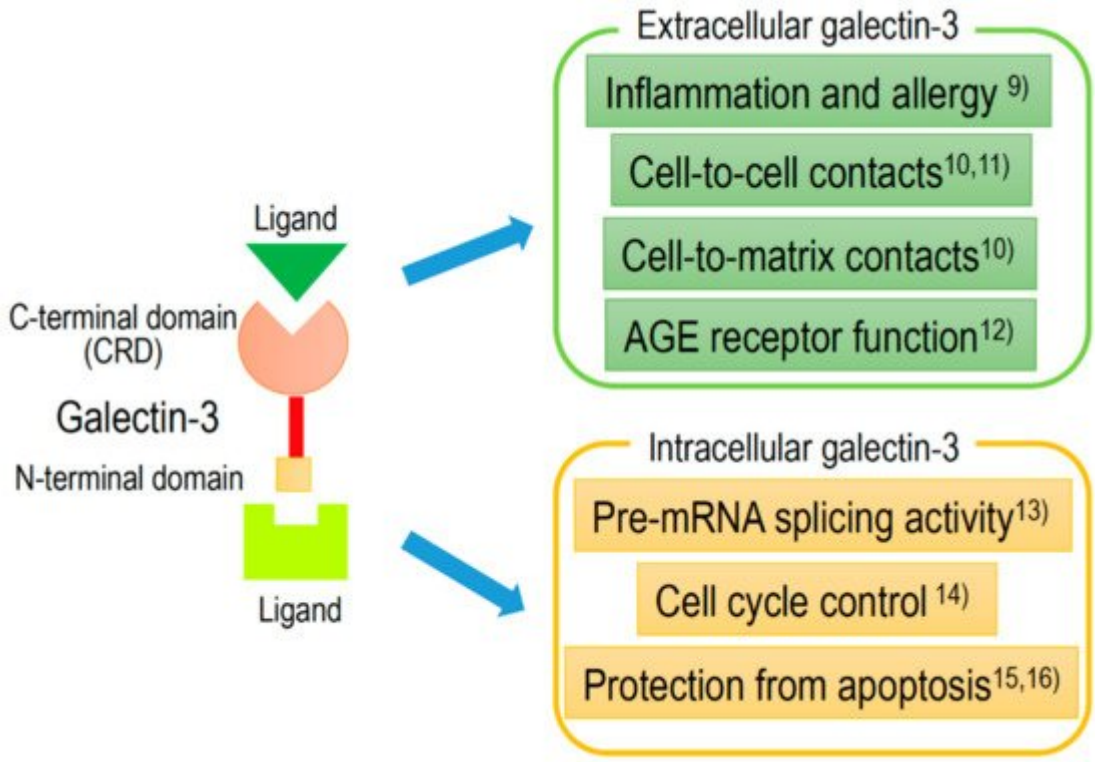

Figure 2. Schematic structure of galectin-3 and the intracellular and extracellular functions.

Recently, Gal-3 has been indicated to be involved in the following broad pathological processes: Inflammation [9], fibrosis, cell-to-cell [10][11] or cell-to-matrix [12] contacts, cell proliferation [13][14], and protection from apoptosis [15][16]. Furthermore, many studies have revealed that Gal-3 expression is detected in many disease conditions, such as heart disease [17][18][19][20][21][22][23], kidney disease [24][25][26][27], diabetes mellitus [24][25][28], viral infection [29][30][31][32], autoimmune disease [33][34][35][36], neurodegenerative disorders [37][38][39][40][41][42], and tumor formation [43][44][45][46][47][48][49][50][51][52].

Since Gal-3 is readily secreted to the cell surface and into biological fluids (e.g., serum and urine), from injured cells and inflammatory cells, Gal-3 may be used as a sensitive diagnostic or prognostic biomarker for various pathological conditions [44][52][53][54]. Furthermore, Gal-3 may also be useful for detecting very early stage of some diseases. Gal-3 has already been used as a novel biomarker in the early detection of myocardial dysfunction and heart failure [55]. Gal-3 has been validated as a biomarker of fibrotic degeneration in acute myocarditis following cardiac viral infection. In an animal model of heart failure, serum Gal-3 levels was shown to be used as an diagnostic biomarker for early detection of cardiac degeneration in acute myocarditis [31] and acute myocardial

infarction [56]. Furthermore, Gal-3 is also a good specific marker for indicating the early stage of glioma tumorigenesis [43].

Serum levels of Gal-3 are usually determined by enzyme-linked immunosorbent assay (ELISA) using commercially available materials [57][58]. The localization or time-course of Gal-3 expression in various organs are examined immunohistochemically using commercially available anti-Gal-3 antibodies [31]. Gal-3 levels may be changed by different clinical factors in patients, depending on the underlying pathological conditions. Some previous studies indicated contradicting results on the association between Gal-3 levels and the prediction of clinical outcomes [59][60][61]. These studies, however, might be limited by the insufficient size of the clinical sample. In this review, we discuss and summarize recent developments of the biomarker characteristics and long-term outcome prediction of Gal-3 in patients with various types of diseases (Table 1) as well as associated animal models (Table 2). Furthermore, we provide an overview of Gal-3 as a next-generation biomarker for detecting early stage of various diseases.

Table 1. Galectin-3 expression in various diseases and potential use as clinical biomarkers.

	Diseases	Usage of Biomarker	Potential Use as Biomarkers	Refs.
Heart disease	acute heart failure	plasma level	combination with natriuretic peptide	[62]
	acute heart failure	plasma level	promising prognostic marker	[63]
	chronic heart failure	plasma level	useful in HF patients with preserved LVEF	[64]
	chronic heart failure	myocardial and plasma level	not associated with histology	[65]
	acute myocardial infarction	serum level	no definite relationship with ventricular remodeling	[66]
Nervous system diseases	myelin degeneration	tissues	activation of the phagocytosis of degenerated myelin	[42]
	intracerebral hemorrhage	plasma level	prognostic predictor	[67]
	subarachnoid hemorrhage	plasma level	prognostic predictor	[68]
	global brain ischemia	cerebrospinal fluid	prognostic marker and inflammatory mediator	[69]
Renal disease	CKD	plasma level	associated with progression of CKD	[25]

	Diseases	Usage of Biomarker	Potential Use as Biomarkers	Refs.
	SLE nephritis	serum and biopsy specimens	associated with SLE patients, particularly in SLE nephritis	[70]
Liver disease	liver fibrosis	serum Gal-3 related binding protein	assessing liver fibrosis	[71]
Connective tissue diseases	rheumatoid arthritis	serum level	increased in early rheumatoid arthritis	[72]
	SLE	serum anti-Gal-3 antibody	a key role in SLE skin lesions	[73]
	systemic sclerosis	serum level	predictor of mortality	[74]
Neoplasms	colorectal cancer	serum and tissues	related to tumor progression	[52]
	breast cancer	human cell lines	important factor for treatment	[75]
	non-small cell lung cancer	tumor expression	promotion of invasion and metastasis	[76]
	lung and prostate cancers	tumor expression	therapeutic target of tumor immunity	[77]
	cervical cancer	tumor expression	targets of multifunctional cancer	[78]

	Animal Models	Experimental Methods	Experimental Findings	Refs.
Heart disease	chronic heart failure	intrapericardial injection of recombinant Gal-3	myocardial fibrosis and its pharmacological inhibition	[80]
	chronic heart failure	intrapericardial infusion of low-dose Gal-3	increased Gal-3 in hypertrophied hearts	[81]
	chronic heart failure	banding of the pulmonary artery	increase of Gal-3 in ventricles	[82]
	acute heart failure	viral myocarditis	time-course analysis of cardiac and serum Gal-3	[31]
Nervous system diseases	multiple sclerosis	EAE in Gal-3-deficient mice	reduction in severity of EAE	[83]
	multiple sclerosis	spinal cord in EAE	Gal-3 observed at early stage before symptoms	[84]
	Huntington's disease	mouse model of Huntington's disease	plasma and brain Gal3 levels correlated with disease severity	[40]
	brain ischemia	time course analysis of Gal-3 in hippocampus	usefulness of early stage of Gal-3 for ischemic brain	[39]
	brain ischemia	temperature-dependent enhancement of Gal-3	hypothermic prevention of Gal-3	[30]

	Animal Models	Experimental Methods	Experimental Findings	Refs.
Renal disease	cerebral infarction	cerebral artery occlusion	up-regulated Gal-3 in late stage of permanent ischemia	[85]
	renal ischemia	Gal-3 deficient mice	less acute renal tubular necrosis	[86]
	renal fibrosis	unilateral ureteral obstruction	renal fibroblast activation by macrophage-secreted Gal-3	[87]
	renal ischemia	unilateral ureteral obstruction	Gal-3 protect renal tubules	[88]
	lipid-induced renal injury	Gal-3 deficient mice	more marked in Gal-3 deficient mice	[89]
Liver disease	NAFLD/NASH	Gal-3 deficient mice	attenuated inflammation and fibrosis	[90]
Connective tissue diseases	SLE	anti-Gal-3 antibody injected into skin	induction of lupus-like histologic changes	[73]
Neoplasms	glioma	analysis of preneoplastic lesions	expressed in preneoplastic lesions	[43]
	ovarian cancer	ovarian cancer xenografted mice.	galectin-3 maintains ovarian cancer stem cells	[91]
	oral cancer	Gal-3 deficient mice	no significant difference	[92]

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3. Gal-3 and Heart Disease

3.1. Clinical Use of Gal-3 as a Possible Biomarker in Heart Disease

Recently, many reports have indicated that Gal-3 is a novel biomarker of heart disease and a prognostic indicator of patients with heart failure.

Clinical studies suggest that serum and myocardial Gal-3 levels in patients with heart failure reflects cardiac inflammatory condition and can be considered as a useful biomarker for both cardiac inflammation and fibrosis, depending on the pathophysiological mechanisms of heart failure [93]. In the general population, a high concentration of plasma Gal-3 correlates with clinical outcomes of heart failure [94][95]. The increased serum levels of Gal-3 are associated with adverse clinical events in both patients with acute [62][63] and chronic [64][65] heart failure with preserved or reduced ejection fraction.

3.2. Established Biomarkers in Heart Disease

Some practical guidelines have indicated the utility of established or newly emerged biomarkers in diagnosis and risk management of heart failure. In fact, American College of Cardiology Foundation (ACC)/American Heart Association (AHA), Heart Failure Society of America (HFSA), and European Society of Cardiology (ESC) have established the natriuretic peptides (NPs), circulating hormones of cardiac origin that play an important role in the regulation of intravascular blood volume and vascular tone, as useful diagnostic biomarkers in the patients suspected of heart failure [96][97][98][99]. However, the utilities of novel biomarkers other than NPs are less established in clinical practice. The recommendations on the clinical assessment and analytical perspectives of novel biomarkers in diagnosis and management of heart failure were prepared by the National Academy of Clinical Biochemistry (NACB) [100]. In these criteria, novel biomarkers need to be able to recognize fundamental causes of heart failure, assess its severity, and foresee the risk of the disease progression. The ACC/AHA guidelines recommended the use of Gal-3 as a biomarker for assessment of myocardial fibrosis in heart failure, however, the ESC has not recommended the clinical use of Gal-3 [101].

3.3. Gal-3 as a Biomarker of Fibrosis

Myocardial fibrosis is tightly implicated in the pathophysiological mechanisms for ventricular remodeling of heart failure. As a potential key factor in pathophysiology of heart failure, US Food and Drug Administration has approved Gal-3 as soluble biomarkers for myocardial fibrosis to detect ventricular remodeling [96]. Thus, the serum levels of Gal-3 are associated with ventricular remodeling and cardiac function. However, whether and how Gal-3 plays a pathophysiological role in cardiac remodeling remains unclear, especially in clinical settings. In fact, the serum levels of Gal-3 was not related to left ventricular remodeling defined by cardiac MRI in patients with acute myocardial infarction and left ventricular dysfunction, although certain biomarkers involved in extracellular matrix formation, such as matrix metalloproteinase-3 and monocyte chemoattractant protein-1, at baseline (mean 46 h), were highly associated [66]. In addition, Sivatsan et al. (NWTDR) conducted a study that found that Gal-3 could not predict mortality, but biomarkers could be used as a predictor of mortality [102].

3.4. Usefulness of Gal-3 in Animal Models

As with present clinical findings, Gal-3 and heart failure have also been studied clinically, however, many animal models clearly demonstrate the possibility of Gal-3 as a novel biomarker of heart disease. Overexpression of myocardial Gal-3 during early pre-symptomatic stages of heart failure has been well documented in several studies using animal models. Intrapericardial injection of recombinant Gal-3 in healthy rats significantly increased the degree of myocardial fibrosis with ventricular remodeling, and the induction of heart failure [80][81]. And Gal-3 was indicated to colocalize with activated myocardial macrophages [80]. On the other hand, cardiac remodeling and dysfunction induced by Gal-3 was prevented by a pharmacological inhibitor of Gal-3, N-acetyl-seryl-aspartyl-lysyl-proline [80]. In a rat model of heart failure, increased Gal-3 was detected at hypertrophied hearts, prior to the development of heart failure [81]. These findings imply that Gal-3, at the early stages of inflammatory responses, may be a potential therapeutic target in the treatment of heart failure. A rat model of right ventricular heart failure, created by banding of the pulmonary artery, demonstrated that Gal-3 was significantly increased in both right and left ventricles and that protein kinase C promoted cardiac fibrosis and heart failure by modulating Gal-3 expression [82]. In order to clarify the important role of myocardial Gal-3 expression during the

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