Review Article

Multi Functional Diagnostic Exploitation of Human Galectin-3

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ABSTRACT

Galectin-3 is a member of the family of animal lectins, which selectively binds β-galactoside residues. Galactin-3 regulates a number of biological processes, including cell differentiation, growth, angiogenesis, embryogenesis, inflammatory responses, cell progression and metastasis. Several studies have shown a correlation between levels of Galectin-3 and tumor progression in liver, thyroid, colon, gastric and breast carcinomas, making Galectin-3 an emerging cancer marker. A major expression of Galectin-3 is found in the colonic epithelium. It is also abundant in the activated macrophages. In the nucleus, Galectin-3 acts as a pre-mRNA splicing factor. It is involved in acute inflammatory responses including neutrophil activation and adhesion, chemoattraction of monocytes macrophages, opsonization of apoptotic neutrophils, and activation of mast cells. These all features make Galectin-3 as multifunctional protein.

Keywords: Galectin-3, tumor progression, angiogenesis, embryogenesis, cell adhesion, splicing factor, apoptosis.

INTRODUCTION

Lectins are classified into families, among which the galectins are ancient and particularly interesting members. Galectins are a growing family of β-galactoside-binding proteins with characteristic of the presence of at least one carbohydrate recognition domain (CRD) of approximately 135 amino acids with affinity for β-galactosides.[1] Galectin-3 is a chimaera-type galectin (29– 35 kDa) which is unique in galectin family with an extended N-terminal domain constituted of tandem repeats of short amino acid segments (a total of 110–130 amino acids) linked to a single C-terminal carbohydrate-recognition domain of about 130 amino acids. Whereas the C-terminal domain is responsible for lectin activity, the presence of the N-terminal domain is necessary for the biological activity of galectin-3.[2,3]

Galectin-3 is located in the cytoplasm, nucleus, on the cell surface, in the extracellular matrix, and in biological fluids and serum.[4,5] Galectin-3 lacks the classical secretion signal sequence and does not pass through the standard ER/Golgi pathway.[4] Still, it can be transported into the extracellular environment via a non-classical pathway.[6] The biological roles of galectin-3 are defined by its cellular localization, which strongly depends on various factors such as cell type, proliferation status, cultivation and neoplastic progression.[7] Cytoplasmic galectin-3 is involved in the modulation of cell proliferation, differentiation, survival and apoptosis. In the nucleus, galectin-3 is involved in pre-mRNA processing and gene transcription. Extracellular galectin-3 mediates cell adhesion through its multivalent properties and ability to bind cell surface glycoproteins and glycosylated contents of the extracellular matrix[8]. Galectin-3 has been detected in activated macrophages, eosinophils, neutrophils, mast cells, epithelium of gastrointestinal and respiratory tracts, kidneys and some sensory neurons.[4,9] Galectin-3 expression has recently emerged as a potential diagnostic and/or prognostic marker of some cancers.[10] This Study emphasize on Galectin-3 which is involves in number of carcinoma condition, cardiovascular disease and different process like cell-cell adhesion, cell-matrix interactions, growth regulation, apoptosis, angiogenesis and mRNA splicing. These observations lead to the recognition of galectin-3 as a multifunctional protein.

Galectin-3 and Cardiovascular Disease

Heart failure affects more than 5 million people in a year, and there are more than 5, 00,000 new cases diagnosed each year.[11] Perhaps best known for its role as a mediator of tumor growth, progression and metastasis,[8,12] a role for galectin-3 in the pathophysiology of heart failure (HF) has been suggested recently. Galectin-3 is a member of the galectin family involved in numerous physiological and pathological processes,[7] some of which, inflammation and fibrosis, are essential contributing pathophysiological mechanisms to the development and progression of HF. Galectin-3 was found to be significantly up-regulated in hypertrophied hearts of patients with aortic stenosis and in the plasma of patients with acute[13] and chronic HF.[14,15] Moreover, the involvement of galectin-3 in the development of fibrosis has also been demonstrated in the heart,[16-19] liver,[20] and kidney.[21,22] Taken together, these observations suggest that galectin-3 may be involved in the development of heart failure. It is speculated that interference of galectin-3 may slow the progression of HF and possibly reduce HF-related illness and death.

Cardiac remodelling is an important determinant of the clinical outcome of HF, as it is linked to disease progression and poor prognosis.[23] Liu[24] showed that the

co-infusion of N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) along with galectin-3 into the pericardial sac, not only inhibited fibrosis and inflammation, but also alleviated cardiac dysfunction. Conventionally, the goal of HF therapy was based on symptomatic relief. However, with the acknowledgement of remodelling as a determinant of the clinical outcome of HF, slowing or reversing the progression of remodelling is now recognized as an important goal of therapeutic interventions. Biomarkers play an increasingly important role in the risk stratification of heart failure patients.[25] Circulating plasma concentrations of B-type natriuretic peptide (BNP, 32 AA) and N-terminal pro-BNP (NT-proBNP, 76 AA) are one of the most commonly used biomarkers in HF and their levels are generally increased in proportion to the severity of the myocardial stretch or overload.[26] However, the applicability of BNP (and NT-proBNP) is limited, as their levels are not directly proportional to cardiac disease process. Thus, to allow a more modified medical management of HF, disease-modifying therapies that inhibit the underlying processes leading to HF or its progression are clearly needed to be complemented with other diagnostic tools currently available. Because galectin-3 has been shown to be up-regulated in hypertrophied hearts, its prognostic value has been evaluated in a number of studies.[14]

Similarly, Milting[15] found significantly elevated plasma galectin-3 levels at the time of mechanical circulatory support. Furthermore, patients who died had significantly higher plasma galectin-3 levels than those who were successfully bridged to transplantation. These all findings strongly supports the original experimental observations that galectin-3 plays an important role in the underlying disease processes and that elevation of galectin-3 is associated with disease progression and poor outcome in HF. Lili Yu demonstrated that inhibition of galectin-3 function by genetic disruption or pharmacological interference pauses the progression of cardiac remodeling. Collectively, the results suggest that galectin-3 may be an attractive target for the prevention and treatment of HF.[27]

Tissue and Cellular Distribution

Galectin-3 is found in a wide range of species and tissues.[7] Similar to other galectins, galectin-3 lacks a secretion signal peptide for classical vesicle-mediated exocytosis, so galectin-3 primarily localized in the cytoplasm and, infrequently, in the nucleus and mitochondria. When secreted into the extracellular space,[28] galectin-3 can interact with cell surface receptors, glycoproteins and initiate transmembrane signaling pathways for different cellular functions. Galectin-3 has been detected in activated macrophages, eosinophils, neutrophils, mast cells, epithelium of the gastrointestinal, respiratory tracts, in the kidneys and some sensory neurons.[5,9] Moreover, galectin-3 displays pathological expression in many tumors, e.g., human pancreas, colon and thyroid carcinomas etc.

It has been shown that in 3T3 mouse fibroblasts, the nuclear versus cytoplasmic distribution of this protein depended on the proliferation state of target cells under analysis. In inactive cultures of fibroblasts, galectin-3 was predominantly cytoplasmic; however, proliferating cultures of the same cells showed intense nuclear staining for this protein. The intracellular location of galectin-3 is connected with its role in the regulation of nuclear pre-mRNA splicing and protection against apoptosis. On the other hand, its extracellular location on the cell surface and in the extracellular environment indicates its participation in cell-cell and cell matrix adhesion.[29]

Galectin-3 as an Inhibitor of Apoptosis

Metastasis is the main cause of death in patients affected by malignant neoplasia. Cumulative studies suggested that tumor metastasis is a multifactor process initially determined by changes in homotypic and heterotypic cell adhesion, apoptosis, evasion of immune responses, angiogenesis, migration and invasiveness.[30] Increased resistance to apoptotic stimuli seems to be an essential for transformation process of cell. One of the earliest examples that increased cell survival plays an important role in lymphomagenesis was the discovery of the anti-apoptotic protein BCL-2 and the increased expression of BCL-2 in follicular lymphoma (FL).[31-34]

Galectin-3 was found to have a significant sequence similarity with the Bcl-2 protein, a well-known suppressor of apoptosis. The lectin contains a four amino acid motif, Asn-Trp-Gly-Arg, which is a highly conserved sequence within the BH1 domain of the Bcl-2 family proteins and is crucial for Bcl-2 protein function in the inhibition of programmed cell death.[35,36] Akahani[34] showed that an amino acid substitution of Gly to Ala at position 182 in this motif of galectin-3 prevents its anti-apoptotic activity.

The four amino acid motif in Bcl-2 is critical for Bcl-2/Bcl-2 homodimerization and Bcl-2/Bax heterodimerization.[37] Yang[36] demonstrated that galectin-3 can interact with Bcl-2 in a lactose-inhibitable manner. This finding is very surprising since Bcl-2 is not a glycoprotein. The authors suggested that the Asn-Trp-Gly-Arg motif is present within the CRD in galectin-3 and is closely involved in interaction with Bcl-2. Lactose binding to galectin-3 may induce a conformational change in the critical region of this protein, which prevents its interaction with Bcl-2. The molecular mechanism by which galectin-3 regulates apoptosis induced by different agents remains to be elucidated.

However, it is possible that this lectin can be mimic Bcl-2 protein. Bcl-2 is a mitochondrial protein located on the outer membranes. It regulates apoptosis by blocking the release of cytochrome c from the mitochondria.[38,39]

Recent results of Dr. Raz clearly demonstrated that galectin-3 expression regulates the apoptotic response of prostate cancer cells to chemotherapy through the mitochondrial apoptosis pathway.[40]

Moon[41] showed that galectin-3 inhibition of nitrogen free radical-mediated apoptosis in human breast carcinoma BT549 cells involved the protection of mitochondrial integrity, the inhibition of cytochrome c release and the activation of caspase. Thus, galectin-3 appears to be a mitochondrial-associated apoptotic regulator as same as Bcl-2.[41,42] Over-expression of galectin-3 in Jurkat T cells protected the cells from Fas- and staurosporine-induced cell death[43] and galectin-3 overexpression in breast carcinoma cells protected the cells from apoptosis induced by *cis*-platin, cyclohexamide, nitric oxide and UV treatments.[35,41,44-46] Overexpression of galectin-3 also prevents human breast carcinoma BT 549 cells from undergoing anoikis, a specific form of apoptosis caused by loss of epithelial cell-matrix interactions.[47,48]

Katrina K. Hoyer have shown that many DLBCL, PEL, MM cell lines and patient samples express abundant Galectin-3. Molecular therapies targeted to avoid the anti-apoptotic effects of galectin-3 could upgrade the progression of selected lymphomas and synergize with existing treatments.[49] Therefore, one can reasonably expect that blocking galectin-3 antiapoptotic function could supplement the cytotoxic effect of chemotherapeutic agents on carcinoma cells. It has also been reported that the nuclear export of phosphorylated galectin-3 regulates its anti-apoptotic activity in response to chemotherapeutic drugs. Certainly anticancer drugs can induce DNA damage, which causes phosphorylated galectin-3 to translocate from the nucleus to the cytoplasm resulting in stabilization of mitochondrial membrane integrity which prevents cytochrome *c* release and subsequent caspase activation, resulting in the suppression of apoptosis and anticancer drug resistance. Finally, it has been suggested that targeting galectin-3 could improve the effectiveness of anticancer drug chemotherapy in several carcinomas.[50]

Carbohydrate Binding

Galectins are a structurally related family of animal lectins defined by two properties: (i) an affinity for β-galactoside sugars; and (ii) a sequence homology which corresponds to the CRD, which is a beta sandwich of about 135 amino acids long and is responsible for β-galactoside binding.[1,10,12,51] Galectin-3 is a unique in the family, having an extra-long and flexible N-terminal domain consisting of 100-150 amino acids, according to species, made up of repetitive sequence of nine amino acid residues rich in proline, glycine, tyrosine and glutamine and lacking charged or large side-chain hydrophobic residues.[4,52-54] The N-terminal domain contains sites for phosphorylation (Ser 6, Ser 12)[55,56] and other determinants important for the secretion of the lectin by a novel, nonclassical mechanism.[28]

Rongyu demonstrated that galectin-3 is a receptor recognizing the major xenoantigen, which leads to monocyte accumulation, one of the major mechanisms leading to delayed xenograft rejection. Galectin-3 could provide another pharmacological target by which delayed xenograft rejection may be inhibited.[57] Structural and mutagenic studies enabled the identification of contact residues in the galectin-3 CRD responsible for recognition of these more complex carbohydrates.[58] Recently, Hirabayashi[59] showed that the N-terminal non-CRD domain contributes to the enhanced affinity of galectin-3 for extended structures of basic recognition units such as Lac or LacNAc (i.e. D-lactosamine & N-Acetyl-D-lactsamine). Frontal affinity chromatography analysis revealed that intact galectin-3 showed an on average 3.8 times higher affinity for oligosaccharides terminated with fucose or sialic acid residues than its deletion product in which the N-terminal domain was removed by Clostridium *hystolyticum* collagenase digestion.

Ligands of Galectin 3

Because of its affinity for polylactosamine glycans, galectin-3 binds to glycosylated extracellular matrix components, including laminin, fibronectin, tenascin and Mac-2 binding protein.[57,60-64] It was also reported that some cell surface adhesion molecules, for example integrins are ligands for galectin-3.[65] Dong purified several glycoproteins from lysates of the murine macrophage cell line that bind to a galectin-3 affinity column. Some of these receptors has labeled after biotinylation of intact cells displaying their location at the cell surface. Dong isolated intact galectin-3-binding glycoproteins from preparative SDS-PAGE or of chemically derived fragments and found several homologies with known proteins by N-terminal amino acid sequencing, immune precipitation with specific antibodies.[65]

Claudia[66] describing the clinical importance of a specific ligand of galectin-3 (i.e., 90k) in human pathology[67,68] and they quantified circulating 90k/Mac-2 ligand (by ELISA) on blood samples obtained from adenomas (AD) and adenocarcinoma (ADK) patients, as well as from healthy donors. Substantial difference was not detected between AD and ADK patients regarding 90k plasma levels. On the contrary, samples obtained from both AD and ADK patients showed significantly higher levels of 90k protein as compared to healthy donors. Interestingly, precise statistical analyses demonstrate a positive correlation between plasmatic values of 90k molecule with respect to galectin-3 expression on the cell surface either in AD or in ADK, and this positive correlation was independent from the type of neoplastic lesion considered (AD or ADK).[66]

Sarafian examined the expression of Lamp-1 and Lamp-2 and their interactions with galectin-3 in different human tumor cell lines. They suggested that Lamps may be considered a new family of adhesive glycoproteins participating in the complex process of tumor invasion and metastasis.[69] Recently it has been shown that MP20, the lens membrane integral protein and a member of the tetraspanin superfamily, also seems to be a ligand for galectin-3.[70] It is not identified exactly what role the MP20/galectin-3 complex could play in the lens. Point mutations in the MP20 gene cause lens vacuolation and fiber cell disorganization shows that MP20 acts in lens

development. It is possible that galectin-3 plays an essential role in modulating the ability of MP20 to form adhesive junctions at this critical stage of development.[70] Apart from extracellular proteins (mentioned above), Galectin-3 is also have an intracellular location and interaction with several proteins inside the cell, i.e., Chrp,[71] CBP70,[72] cytokeratins,[73] Gemin4,[74] Bcl-2[35] and Alix/AIP-1.[75]

A carbohydrate binding protein with size 70 kDa (CBP70) is a nuclear and cytoplasmic lectin protein glycosylated by the addition of N- and O-linked oligosaccharide chains.[76] In this cellular compartment, CBP70 interacts with galectin-3 via a protein-protein interaction mediated by the addition of lactose, probably resulting in modification of the galectin-3 conformational structure. Menon[71] used yeast two-hybrid system to search for cytoplasmic proteins and found some novel protein was shown to bind galectin-3 in a carbohydrate-independent manner. The novel protein contains an unusually high content of cysteine, histidine residues and shows substantial homologies with several metal ion-binding motifs present in known proteins. This protein has been referred to as a cysteinehistidine rich protein – Chrp. The interaction between galectin-3 and Chrp was confirmed by immunoprecipitation and *in vitro* binding assays.[77] Vlassara[78] was the first to propose that galectin-3 is one of the progressive glycation end products (AGE) receptors. They define the identification of the polypeptide currently termed galectin-3 as a macrophage cell membrane protein which exhibits high-affinity binding for non-enzymatically glycated (AGE)-modified proteins and that facilitates covalent complex formation with these ligands. Galectin-3 was identified as an AGE-binding protein in astrocytes, macrophages and umbilical vein endothelial cells.[79]

Galectin-3 and Tumors of Nervous System

Galectins are known to play an important role in cancer malignant progression.[12] Galectin-3 has been reported to bind, *in vitro* to a number of neural recognition molecules.[63] Because this protein has been involved in homotypic and heterotypic cellular adhesive interactions that play a role in tumor progression and metastasis.[80] Researcher has examined the expression of galectin-3 in primary human brain tumors and in metastases to the brain. The results demonstrate that galectin-3 is expressed in human brain tumors and its expression correlates with the malignant potential of tumors in the central nervous system (CNS). There is a relationship between the level of expression of galectin-3 and the level of malignancy in human gliomas.[81-83] Bresalier[81] showed that normal brain tissue and benign tumors did not express galectin-3 but anaplastic astrocytomas (grade 3) and glioblastomas (grade 4 astrocytomas) respectively exhibit intermediate and high expression. Moreover, reported a more significant expression of galectin-3 in metastases than in the primary tumors. They showed that the expression level of galectin-3 was significantly associated with astrocytic tumor grade.[81] Different results were found by Gordower[82]. They showed that the level of galectin-3 expression significantly decreases in the majority of tumor astrocytes, from low to high grade astrocytic tumors. However, the authors suggested that human astrocytic tumors are very heterogeneous, and in spite of the general decrease in the level of galectin-3 expression, some tumor cell clones express a higher level of galectin-3 with increasing level of malignancy.[82] In alternative study, galectin-3 expression was found to be significantly higher in glioblastomas and pilocytic astrocytomas than in oligodendrogliomas, anaplastic oligodendrogliomas and diffuse astrocytomas.[84] Finally, it was reported that galectin-3 was expressed in human oligodendrocytes, endothelial cells and macrophages/microglial cells in areas of solid tumor growth.[85] Strik have used immune histochemistry to identify the cellular origin and extent of galectin-3 positivity in glioma samples.[86] They have shown that galectin-3 was expressed in neoplastic astrocytes, macrophages/microglial cells, endothelial cells and some B- and T-lymphocytes.

The regulation of galectin-3 expression by Runx-2 has been recently suggested to contribute to the malignant progression of glial tumor. Runx2 is a member of the Runx family of transcription factors expressed in a variety of human glioma cells, whose expression pattern in these cells strongly correlates with that of galectin-3, but not with that of other galectins. Knockdown of Runx2 was shown to be accompanied by a reduction in both galectin-3 mRNA and protein levels by minimum of 50%, dependent on the glial tumor cell line tested.[87] A further study suggested that galectin-3 is involved in tumor astrocyte invasion of the brain parenchyma, since its expression is higher in the invasive parts of xenografted glioblastomas than in their less invasive parts.[83] These all results suggest the involvement and correlation of Galectin 3 and tumor progression and metastasis in nervous system.

Galectin-3 in Head and Neck Carcinoma

More than 500,000 new cases of head and neck cancer are reported per year and the incidence is increasing. Laryngeal squamous-cell carcinoma (SCC) is the most common head and neck cancer which representing about one third of all cases.[88] Galectin-3 is involved in the malignancy of tumor cells, including cancers of the head and neck region.[89] Choufani studied the expression of galectin-3 and the expression of ligands for this lectin in 75 cases of head and neck squamous cell carcinomas (HNSCCs) and in 40 normal tissue specimens. The results showed that HNSCCs exhibited a significantly lower amount of galectin-3 and its ligands than their corresponding normal counterparts.[90] A decrease in the extent of galectin-3 expression correlates with an increasing level of clinically detectable HNSCCs aggressiveness. Further studies confirmed the correlation of galectin-3/galectin-3 ligand levels with a low

differentiation status which is known as an indicator of the recurrence rate in HNSCCs.[91]

Squamous cell carcinoma of the tongue (TSCC) is one of the most common malignant tumors in the oral cavity and accounts for approximately 30%[92] of all total oral cancers. Dong Zhang showed that Galectin -3 inhibition reduces the migration and invasion capacities of the tongue cancer cell lines SCC-4 and CAL27.[93] During the progression from normal cells to cancerous cells, it has been shown that galectin-3 expression markedly decreased in the nucleus and increased in the cytoplasm in tongue cancer.[94] Recently, Lefranc showed that rapidly recurring craniopharyngiomas also have a significantly lower level of expression of galectin-3 than nonrecurring or slowly recurring cases.[95] On the other hand, the level of expression of galectin-3 is correlated positively with the level of apoptosis in human cholesteatomas.[96] Cholesteatoma can invade neighboring tissues and often recurs even after surgical resection. The level of apoptosis is an indicator for the prediction of the recurrence. It is suggested that an up-regulation of galectin-3 expression, which is associated with pronounced apoptotic activity, could have a physiologically protective effect against the substantial apoptotic features occurring in recurrent cholestestomas.[96] Furthermore, cytoplasmic expression of Galectin-3 was detected in approximately 90% of tongue cancers, which correlated with severity and metastasis in tongue malignancies.[97] These all finding strogly supports the correlation between expression of galectin-3 with head and neck carcinoma, which can be used as prognostic marker.

Galectin-3 and Thyroid Carcinoma

Thyroid cancer represents one of the few types of cancer that remain has a diagnostic dilemma for the clinician and doctors. Thyroid nodules are extremely common in the general population, being identified in 5% of patients by palpation and 50% by ultrasound examination.[98] Fine needle aspiration biopsy (FNAB) represents the critical initial diagnostic test used for evaluation of thyroid nodules. Galectin-3 expression has been recently detected in human thyroid carcinomas, but not in benign tumors or normal tissue. Galectin-3 is highly expressed in thyroid carcinoma of follicular cell origin, whereas neither normal thyroid tissues, nodular goiters nor follicular adenoma express galectin-3 in human[99-101]. In addition, it is observed that galectin-3 mRNA was present in all malignant thyroid lesions, where as it is not detectable in normal and non-malignant tissues.[101]

According to Kawachi[102] Galectin-3 down-regulation in papillary thyroid carcinoma may promote the release of some tumor cells from the primary tumor, resulting in metastasis. Fine needle aspiration cytology (FNAC) of the thyroid is a rapid, minimally invasive, and cost-effective first screening for patients with thyroid nodules.[103] With regard to papillary carcinomas, Galectin-3 immunohistochemistry can provide a sensitive and reliable approach in the preoperative diagnosis by FNAB.[104,105] A trend towards a stronger expression of galectin-3 in the observed stages of medullary thyroid carcinoma was also detected.[106] On the other hand, expression of galectin-3 in the lymphatic metastases of papillary carcinoma appeared to be significantly lower than in corresponding primary lesions.[102] In the case of medullary thyroid carcinoma, galectin-3 expression was also reduced markedly in lymph node metastases as compared to corresponding thyroid tumors.[107]

Different experimental observations permit the conclusion that expression of galectin-3 in cytoplasm is a phenotype associated with malignant transformation and progression toward metastatic potential.

Galectin-3 and Pituitary Cancer

Recent studies have implicated dysregulation of cell cycle genes, including $p27^{Kip1}$ (p27) and $p16^{INK4A}$ (p16) in the pathogenesis of pituitary tumors.[108,109] The levels of p27 protein are substantial decreased in many carcinomas as compared to normal tissues, and these changes are having prognostic significance, suggesting that this cyclin-dependent kinase inhibitor may have tumor suppression activity.[110-112] Katharina H. Ruebel[113] have recently reported that galectin-3 is expressed in anterior pituitary cells and tumors and its expression was limited to adrenocorticotropic hormone (ACTH) and prolactin-producing tumors.[114] Kadrofske examine the mechanisms of regulating galectin-3 expression in normal and neoplastic pituitaries, and analyzed the LGALS3 gene[115] for possible genetic and epigenetic alterations including the methylation status of the promoter region. They found that, CpG island methylation in the LGALS3 promoter region of a significant percentage of tumors which did not express galectin-3 protein indicating that epigenetic regulation is important in galectin-3 expression in pituitary tumors.

Dominik Riss[114] investigated the role of galectin-3 in the development and progression of pituitary tumors. Immunohistochemical and western blot analysis of normal and neoplastic human pituitaries showed that only prolactin cells (PRL), corticotroph (ACTH) hormone-producing cells and tumors expressed galectin-3. RNA interference experiments were conducted to examine the role of galectin-3 in pituitary cell function. Inhibition of expression of galectin-3 gene by RNA interference decreased HP75 cell proliferation and increased apoptosis.[116] These results indicates the important role of galectin-3 in pituitary cell proliferation and it may serve as a possible therapeutic target to prevent pituitary tumor progression and carcinoma development because of the poor prognosis associated with pituitary carcinomas.

Galectin-3 in Breast Carcinoma

In steroid-sensitive breast cancer cells, it was suggested that estradiol and progestin might act as coordinates regulating specific genes, including up-regulation of expression of galectin-3, leading to metastatic

phenotype.[117] It was shown by immunohistochemical methods that normal breast tissue expressed a high level of galectin-3 and the expression of galectin-3 protein was down-regulated in breast cancer.[118,119] The introduction of galectin-3 into null-expressing nontumorigenic BT-549 cells resulted in the acquirement of tumorigenicity and property of anchorage-independent growth, suggesting a relationship between galectin-3 expression and malignancy of human breast cancerous cell lines.[120] Honjo[121] determined that the blocking of galectin-3 expression in highly malignant human breast carcinoma MDA-MB-435 cells lead to the reversion of the transformed cellular phenotype and to significant suppression of tumor growth in nude mice. So they suggested that the expression of galectin-3 is necessary for the maintenance of the transformed and tumorigenic phenotype of MDA-MB-435 breast carcinoma cells.

Galectin-3 expressed on the endothelial cell surface has been shown to promote adhesion of breast cancer cells to the endothelium by interaction with cancer- associated Thomsen-Friedenreich (TF) antigen cell surface molecules.[122,123] These findings indicate an involvement of galectin-3 in malignant progression of breast carcinomas and suggest a possibility that galectin-3 may serve as a potential molecular target for therapy of carcinomas harboring overexpressed galectin-3.

Galectin-3 and Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is currently the fourth leading cause of death by any cancer.[124] Pancreatic cancer is characterized by very aggressive growth with early development of metastases in lymph nodes and distant organs.[125] It is reported that silencing of galectin-3, diminishes the migration and invasion ability of pancreatic cancer cells through the degradation of β-catenin.[126] In addition, oncogene mutations, e.g., of K-ras, and mutations in tumor suppressor genes such as p53 are also commonly found in pancreatic cancer.[127,128] These findings indicate that alterations in the expression of growth factors, growth factor receptors, and K-ras and p53 mutations are important pathophysiological mechanisms that appear to give pancreatic cancer cells a fundamental growth advantage.[129,130]

Considerable effort has been made to understand the molecular changes which may determination the pathogenesis of PDAC. Among the numerous molecular mutation identified in PDAC, mutations in the pro-oncogene K-Ras are found in almost all cases[131] and this is an early event for the PDAC development.[132] They suggested that K-Ras mutations alone are not sufficient for the development of PDAC, additional factors are required to contribute to Ras activity; however, the mechanisms by which Ras activity is further activated are largely unknown. Several studies have indicated that galectin-3 mRNA is up-regulated in pancreatic tumor tissues compared to normal sample[133-135] and transient suppression of galectin-3 has been reported to induce pancreatic cancer cell migration and invasion.[126] Wang found that galectin-3 was also up-regulated in chronic pancreatitis and demonstrated that it was involved in both extracellular matrix (ECM) changes and ductal complex formation.[137]

Shumei Song systematically evaluated the expression of galectin-3 in 120 paired human pancreatic tissues from normal pancreas, pancreatitis and pancreatic tumors, and for the first time determined the expression of galectin-3 in tissues and tumor cells derived from of a mutant K-Ras mouse model of pancreatic cancer. Galectin-3 expression was increased in pancreatic cancers tissue and cancer cells, stimulated pancreatic cancer cell proliferation, invasion and promoted tumor growth. Galectin-3 binds Ras and enhances Ras activity and down-stream signaling.[138] These observations support the conclusion that galectin-3 would be a potential unique target for PDAC.

Galectin-3 and Colorectal Carcinoma

Different studies demonstrated that colon carcinoma cells with high expression of galectin-3 also have high concentration of MUC2 mucin, whereas those with low galectin-3 levels have low MUC2 concentration, and that galectin-3 plays an important role in metastasis and progression of colon carcinoma.[139-141] MUC2 mucin is a major secreted product of the gastrointestinal tract[142] that is thought to be a major ligand for galectin-3 protein.[143] The close relationship of MUC2 mucin and galectin-3 is seems to be one basis for the correlation of galectin-3 levels with metastasis and progression in colorectal carcinoma.

Recent studies have shown that a cancer associated glycoform of haptoglobin is a major circulating ligand for galectin-3 in the serum of patients with colon carcinoma.[144] Haptoglobin is distinct from mucin and carcinoembryonic antigen (CEA). Galectin-3, a novel CD 95-binding partner, modulates the CD95 apoptotic signal transduction pathway[145] which indicates that galectin-3 may contribute to the progression of colorectal carcinoma in mechanisms independent of MUC2 mucin. Kazuya Endo[146] indicated that galectin-3 expression is significantly related to various clinicopathological factors, specifically lymph node metastasis, lymphatic permeation, tumor size, tumor depth, venous invasion, pathological type, distant metastasis and Dukes stage. Moreover, expression of galectin-3 is an independent prognostic factor linked with lymph node metastasis and Dukes' stage. A valid explanation of the above result comes from the close relationship between galectin-3 expression and MUC2 mucin expression.

Immunohistochemical assessment of galectin-3, β-catenin and Ki-67 expression was performed on colorectal cancer patients; found the reduction of galectin-3 expression is associated with the invasion and metastasis of colorectal cancer.[147] It was found that colorectal tumor progression is associated with a decrease in the galectin-3 expressions in early stages and an increase in the cytoplasmic

compartment dissociated from the nuclear staining in later stages.[148] It was suggested that galectin-3 may express its malignant property through regulation of apoptotic signal transduction by interacting with its ligands. In addition to mucins, the ligands identified in colon cancer include Mac-2-binding protein, carcinoembryonic antigen (CEA), lamp 1 and lamp 2 glycoproteins and haptoglobin related proteins.[144] Of those ligands, haptoglobin-related protein has been reported as a major circulating ligand for galectin-3, and is elevated in the serum of patients with colon carcinoma but not in healthy person. This all findings supports that detection of galectin-3 in serum and its ligand may serve as clinically useful tumor markers.[144]

Renal Cell Carcinoma and Renal Failure

Renal cell carcinoma (RCC) accounts for around 3% of all adult malignancies and its incidence rate is increasing per year.[149] Galectin-3 expression has also been recently identified in some RCCs by complementary DNA microarray studies in human renal carcinoma.[150] It has been reported that, strong expression of galectin-3 was observed in case of renal neoplasms (42.4%). Although 95.7% oncocytomas and 90.5% chromophobe RCCs express galectin-3, only 12.5 % papillary RCCs and 34.3 % clear cell RCCs express galectin-3.

This study confirms that Galactin-3 is strongly overexpressed in renal cell neoplasms of distal tubular differentiation, that is, oncocytoma and chromophobe RCCs, suggesting it might be used as a possible differential diagnostic tool for renal cell neoplasm with oncocytic or granular cells.[151]

Manabu Sakaki demonstrated the expression of galectin-3 in clear cell renal cell carcinoma (CC-RCC) by evaluate different kidney cancer cell lines Caki-1, Caki-2, A704, ACHN and KPK-1 for the expression of galectin-3.

They conclude that galectin-3 is highly expressed in CC-RCC, especially in CC-RCC with distant metastasis, suggesting that galectin-3 may serve as a novel target molecule for predicting CC-RCC metastasis.[152]

Junichiro Nishiyama found that galectin-3 mRNA level was elevated in ischemia/reperfusion renal failure and there was a highly significant correlation between galectin-3 expression and renal injury. Additionally, up-regulation of galectin-3 mRNA was also shown in folic acid-induced acute renal failure (ARF). They speculate that galectin-3 plays an important role in pathophysiology of acute renal injury.[153]

Galectin-3 and Prostate Carcinoma

In prostate cancer, galectin-3 expression was reported to be down-regulated with progressive stages of carcinoma.[154-157] While in many other carcinoma condition such as thyroid, gastric carcinoma, and squamous cell carcinoma of the head and neck, galectin-3 expression was up-regulated with increased malignant phenotype charecterstic.[158-160] Immunohistochemical and western blot analysis showed a generally reduced expression of galectin-3 in prostate cancer relative to the level in normal human prostate tissue.[154,155] It has been found that galectin-3 is present in human cell lines PC-3M, PC-3, DU-145, PrEC-1, and MCF10A. Galectin-3 was not detected in TSU-pr1 and LNCaP cells by western blot analysis. Further studies demonstrated that approximately 60–70% of the normal tissue shows heterogenous expression of galectin-3. However, in stage II and III tumors, there was a dramatic decrease in galectin-3 expression in both prostate intraepithelial neoplasia (PIN) and tumor sections.[155]

Van den Brule studied on subcellular expression of galectin-3 in primary human prostate carcinomas using immunohistochemistry.[161] They found a clear change in the location of galectin-3 in prostate carcinoma cells as compared with normal cells.

Commonly, normal glandular cells expressed galectin-3 in both nucleus and cytoplasm. In case of malignant lesions, galectin-3 was expressed in the cytosol but was generally excluded from the nucleus. Such a distribution of galectin-3 was correlated with malignancy progression. These results suggest that galectin-3 might have anti-tumor activities when present in the nucleus, whereas it could favor tumor progression when expressed in the cytoplasm.[161]

CONCLUSION

Routine galectin-3 measurement in patients with heart failure may provide important novel clinical utility. In conjunction with BNP and NT-proBNP, galectin-3 may be used to identify those patients at highest risk for readmission or death, thus allowing the physician and clinician to care the individual patient as desired.

Galectin 3 having affinity for polylactosamine glycans and it binds to number of extracellular and intracellular protein. This feature can be used for the purification of different proteins and antibodies of human interest using affinity column made up with Galectin-3. In human, galectin-3 expression was reported to be down-regulated with progressive stages of some carcinoma conditions e.g. prostate cancer. Whereas in many other carcinoma such as thyroid, gastric carcinoma, and squamous cell carcinoma of the head and neck, galectin-3 expression was up-regulated with increased malignant phenotype.

These all results indicated that galectin-3 is a multifunctional protein engaged in different biological events.

The abundance of information concerning galectin-3 expression and its ligands enables us to see mechanisms of basic cellular processes such as adhesion, proliferation, signal transduction, mRNA splicing and apoptosis in a new light. It is possible that in the near future, galectin-3 may become an attractive target for the development of new strategies in the diagnostics and treatment of some diseases especially cancers and cardiovascular disease.

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