

MINI REVIEW

Galectin-1 As a Predictive Biomarker in Cancer

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ABSTRACT

Aim: A key development in oncology has been the discovery of galectins and their role in cancer growth, progression and metastasis. Early clinical studies evaluated the utility of galectin-1 as promising novel biomarkers in cancer diagnosis.

Background: Galectin-1 is the most studied member in the family of galectins and has been implicated in various tumorigenic processes. Thus, the potential of galectin-1 as a cancer biomarker in many malignancies and how this novel marker modality may affect patient outcomes in the future needs to be discussed.

Review Results: Various experimental and clinical data demonstrate a correlation between galectin-1 expression and tumour development, and therefore, galectins may have the potential to serve as reliable tumour markers in cancers.

Conclusion: The unique role played by the galectin-1 protein in carcinogenesis and its established role in the process of carcinogenesis demands further large cohort and cross-sectional studies to validate its use as a biomarker.

Clinical Significance: In most malignancies, there is an increased serum level of galectin-1 which demonstrates its plausible use as a potential novel biomarker in oncology, which can be used both for diagnosis and prognosis of the disease.

Key Words: Biomarker, Galectin-1, Carcinogenesis, Prognosis

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In 1976, Galectins were isolated from various sources like chick muscle, calf heart and lungs. Since then, 16 members of the family have been identified and named in the order of their discovery. Structurally each galectin has evolutionarily conserved carbohydrate recognition domains (CRD) with an affinity for β -galactose-containing glycoconjugates. They are designated according to the number and structure of these CRDs as a prototype, tandem repeat and chimeric galectins. Prototype galectin is a monovalent galectin containing one CRD capable of homodimerizing to become functionally bivalent. Galectins -1, -2, -5, -7, -10, -11, -13, -14, -15 and -16 are all prototypic galectins. Tandem repeat galectins are bivalent galectins having two non-identical CRDs connected by a peptide linker, with galectins -4, -6, -8, -9 and -12 falling under this category. They are also called “heterodimeric” because of their distinct CRDs. Chimeric galectins consist of one CRD bearing an extended N-terminal domain with unusual

proline-, glycine-, and tyrosine-rich repeats. Galectin-3 is the only chimeric galectin identified in vertebrates. In terms of species distribution, Gal -1, -2, -3, -4, -7, -8, -9, -10, -12, -13 and -16 are present in humans, Gal -5 and -6 in rodents and Gal -11, -14, and -15 have been isolated from sheep and goats. Galectins are usually produced on free poly-ribosomes and are primarily present in the cytoplasm but are often transported between the cytoplasm and nucleus. Galectins are also expressed on the cell surface and in the extracellular matrix. Intracellularly, they are involved in the regulation of proliferation and apoptosis and facilitate pre-mRNA splicing. The galectins mediate cell-to-cell and cell-to-matrix interactions due to their presence within and on

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the cell's extracellular matrix, which depends on the glycosylation patterns of the cells. These glycosylation patterns, in turn, reflect the underlying biochemical condition of a cell, such as its nutritional state and availability of carbohydrate precursors. There is dysregulated synthesis and degradation of various galectins in tumorigenesis as carcinogenesis is a complex and multifactorial process that depends on the interaction between genotoxic insults, external cellular pressures, and tissue microenvironment. Galectins have been implicated in various biological functions, including homeostasis, apoptosis, vascular embryogenesis, and pathological conditions such as preeclampsia, inflammation, diabetes, atherosclerosis, and cancer.

Galectin-1 (Gal1) Structure

Of the 16 galectin family members, galectin-1 seems to be the chief player in cancer biology and, therefore, has encouraged significant research interest. Galectin-1 is encoded by the LGALS1 gene located on chromosome 22q12. The 0.6 kb transcript results from the splicing of four exons and encodes for a protein of 135 amino acids. Gal-1 is a 14 KDa monomer or a non-covalent homodimer with one CRD per subunit. The dimer is maintained by hydrophobic interactions at the monomeric interface and the well-defined hydrophobic core. The presence of more than one CRD in the homodimer makes it suitable for mediating cell adhesion, triggering intracellular signalling and forming multivalent lattices with cell surface glycoconjugates. The monomeric units are attached so that the 2 CRDs are located at a distance of about 5 nm on opposite ends of the quaternary structure. Each CRD can accommodate a tetrasaccharide. The opposing CRDs initiate cellular recognition and signal transduction events by binding suitably glycosylated ligands. In the extracellular space, homodimers can connect several membrane-receptors enabling cell signalling and cell-cell interactions and letting homotypic and heterotypic aggregation. Each galectin-1 monomer contains six cysteine residues per subunit, conferring a strong sensitivity to oxidation. The cysteine residues must be in a reduced state to maintain a molecular structure with lectin activity since oxidized galectin-1 lacks its lectin activity. Furthermore, oxidized galectin-1 was shown to have cytokine-like behaviour. During oxidation, intramolecular disulfide bridges formed on the galectin-1 structure induce significant conformational changes,

preventing dimerization and ligand recognition.

Galectin-1 Synthesis and Secretion

As is characteristic of cytoplasmic proteins, galectin-1 possesses the typical acetylated N-termini and lacks signal peptides and is synthesized on cytosolic ribosomes. From the cytosol, it can be directed to cell nuclei, translocated to the intracellular side of cell membranes, or secreted. Secretion occurs through an unorthodox mechanism that involves direct translocation across the plasma membrane, bypassing the classical vesicle-mediated endoplasmic reticulum/Golgi pathway for exocytosis. Extracellular galectin-1 has a slightly higher molecular weight (15 kDa) than the 14 kDa form found in cell lysates, suggesting that the secreted galectin-1 undergoes further post-translational modifications before or after secretion. In addition - extracellular galectin-1 (15KDa) binds to cell surfaces at specific locations. Since galectin-1 lacks the signal peptide for secretion pathways, it is suggested that post-translational modifications, resulting in the high galectin-1 molecular mass, are required for galectin-1 export to the extracellular compartment. Galectin-1 secretion depends on functional interactions between the lectin and β -galactoside containing cell surface receptors.

Galectin-1 as a predictive biomarker

Several studies have noticed an upregulated galectin-1 expression in various cancer cells compared to healthy cells. Many epithelial tumours overexpress this protein, including breast, colon, and thyroid cancer, where galectin-1 correlated with tumour aggressiveness and the acquisition of a metastatic profile. Compelling evidence collected over recent decades indicates that galectin-1 upregulation can dramatically impact tumour progression given its pleiotropic roles in cell proliferation, transformation, adhesion, angiogenesis, invasiveness, and immunosuppression. Furthermore, this protein is involved in the adhesion to the extracellular matrix of cells in hepatocellular carcinoma, melanoma, ovarian, and prostate cancer. The increased galectin-1 expression has been reported in the colon, breast, lung, head and neck, ovarian and prostate carcinomas, gliomas, Kaposi's sarcoma, myeloproliferative neoplasia and Hodgkin lymphoma. Besides, galectin-1 is overexpressed in cancer-associated endothelial cells and the stroma surrounding tumor cells. Extracellular galectin-1 has also been detected in the plasma

of numerous tumours and is elevated in patients with poor prognoses of colorectal or head and neck squamous cell carcinomas (HNSCC). Similar findings in Kaposi's sarcoma, colon, breast, prostate and gastric cancer support the correlation between galectin-1 expression and survival, highlighting the significance of this lectin as a possible biomarker or therapeutic target in cancer. The role of Galectin-1 in various malignancies has been further discussed below.

Galectin-1 in pancreatic cancer

The proteomic analysis of pancreatic ductal adenocarcinoma compared to normal tissue demonstrated that galectin-1 expression highly correlates to tumor histology and stage. Studies in pancreatic tumours indicated significantly higher levels of galectin-1 in poorly differentiated and invasive tumours compared to differentiated tumours or normal adjacent tissue. A study demonstrated that the measurement of Galectin-1 levels by ELISA is a novel method for improving pancreatic ductal adenocarcinoma (PDA) diagnosis, which could eventually predict the prognosis of patients with unresectable tumors. In addition, high Galectin-1 levels in blood from PDA patients suggest that it could be a valuable marker for patient follow-up, e.g., for detecting recurrence after surgery and evaluating tumor response during chemotherapy or chemo/radiotherapy, as reported for other tumor types. Studies in pancreatic tumours indicated significantly higher levels of galectin-1 in poorly differentiated and invasive tumours compared to differentiated tumours or normal adjacent tissue.

Galectin-1 in gastric cancer

Gal-1 plays a vital role in human gastric cancer invasion and metastasis. Galectin-1 promotes metastasis in gastric cancer through a Sphingosine-1-phosphate receptor-1 (S1PR1) dependent mechanism. Gal-1 functions in an autocrine manner to induce the epithelial-mesenchymal transition (EMT) in gastric cancer cells in vitro and also enhances the tumorigenic and metastatic capacities of gastric cancer cells in vivo. The cross-talk between Gal-1 and other signalling pathways could play an important role in gastric cancer invasion and the EMT. Gal-1 has been reported to be an independent prognostic indicator of poor survival in gastric cancer, and overexpression of Gal-1 enhances the invasiveness of gastric cancer cells. Recent studies in

gastric cancer showed a positive correlation between galectin-1 expression and tumor stage, tumor invasion and lymph node metastasis. In addition, galectin-1 expression is positively associated with vascular endothelial growth factor VEGF expression, and both can serve as independent prognostic indicators of poor survival for gastric cancer after gastrectomy.

Galectin-1 in breast cancer

In a galectin profiling study, gal-1 showed overexpression in all breast cancer cell lines tested. Microarray analysis comparing breast cancer cell lines with either low or high ERBB2 (HER2/neu) expression identified gal-1 as the most upregulated gene. Increased gal-1 binding was associated with positive lymph node status and the tumour size and stage of breast cancer patients. High gal-1 expression in tumour cells and tumour stroma of breast adenocarcinomas compared with benign breast hyperplasia. The increasing numbers of gal-1-positive cancer cells are also positively associated with the histological grade. Finally, several studies employing different proteomic approaches also point towards the involvement of gal-1 in breast cancer, even in males. The serum of breast cancer patients does contain more gal-1-binding glycoproteins. The increased levels of gal-1 stay confined to the tumour tissue where the protein exerts its function. The quantitation of galectin-1 binding glycoforms could discriminate sera from patients with established metastatic cancer and sera of healthy controls.

Galectin-1 in prostate cancer

Galectin-1 expression in prostate cancers showed that galectin-1 was expressed in most cases of all four histologic types, accumulated in the stroma of the malignant tissue and aggressiveness of the tumor, indicating a significant role of galectin-1 in the acquisition of the invasive phenotype. Gal-1 is the most amply expressed galectin in prostate cancer tissue and is markedly upregulated during disease progression. Gal-1 expression in prostate cancer tissue arrays correlated with the presence of angiogenesis, particularly in advanced stages of the disease. Silencing Gal-1 expression in human prostate cancer cells reduced tumor vascularization without altering the expression of other angiogenesis-related genes. Expression levels of Gal-1 are associated with the growth and metastatic properties of the tumours of prostate and may correlate with a poor

prognosis.

Galectin-1 in thyroid cancer

The expression pattern of galectin-1 in thyroid cancer tissues indicates that these proteins can be useful biomarkers in thyroid cancers. Saussez et al. [21] pointed out the diagnostic value of galectin-1 as a serum and cytological biomarker of papillary carcinoma (PC) and anaplastic carcinoma (AC). Galectin-1 discriminated the malignant nodules from the benign ones with 80% sensitivity and 97% specificity, respectively. Also, the expression of galectin-1 can help to distinguish between poorly differentiated tumors and well/moderately differentiated tumors. Considering that many of the current serum or histological biomarkers overlap both benign and malign lesions, there is an increasing demand for molecular biomarkers able to discriminate a benign thyroid nodule from a thyroid carcinoma.

Galectin-1 in lung cancer

Galectin-1 overexpression in lung adenocarcinoma promotes tumor invasion and metastasis by increasing the expression of matrix metalloproteinases, including MMP-1 and MMP-9, and reorganizing the cytoskeleton. Studies conducted on the effect of galectins in the pathogenesis, aggression and response to treatment in lung cancer have shown a significant role of Gal-1 in tumor progression (18). The association of Gal-1 with integrin $\alpha 6\beta 4$ and Notch1/Jagged2 resulted in enhanced invasion and migration of lung cancer cells. Silencing Gal-1 decreased invasion, migration as well as increased sensitivity to chemotherapy (19,20). Gal-1 gene knockdown studies demonstrated increased survival in lung cancer-bearing mice (19). A recent study by Carlini et al. examined 103 stage I-III non-small cell lung cancer (NSCLC) patients and found that a higher level of Gal-1 correlated with a worse prognosis. In another study, patients showing high Gal-1 expression evidenced a poorer clinical outcome. Thus Gal-1 expression may be a useful biomarker for better prediction of the clinical outcome and management of NSCLC patients.

Galectin-1 in Neuroblastomas

In neuroblastomas, increased Galectin-1 expression was found to be elevated in tissue. Galectin-1 expression correlated with stage, histology, bone marrow metastasis, and poor survival in neuroblastoma patients. Serum

galectin-1 levels were higher in newly diagnosed patients with neuroblastoma than in healthy subjects. Patients with elevated serum Galectin-1 through treatment cycles correlated with the poor chemo responses and tended to have worse outcomes, such as metastasis or stable tumour size, whereas gradually decreasing serum Galectin-1 levels correlated with no observed progression in clinical symptoms. Thus tissue and serum Galectin-1 levels were associated with adverse clinical features in patients with neuroblastoma, and hence serum Galectin-1 could be a potential biomarker for monitoring therapy.

Galectin-1 in gliomas

Galectin-1 considerably affects glioma development. The levels of galectin-1 changes during the progression of malignancy. The galectin-1 expression is present in all types of human gliomas, with no prominent differences between astrocytic, oligodendroglia and ependymal tumors. It's only the grade of astrocytic tumors which correlates with the level of galectin-1. High-grade astrocytic tumors from patients with short-term survival periods have stronger immunopositivity than tumors from patients with long-term survival. Studies have demonstrated a significant relationship between increased galectin-1 expression and poor prognosis in patients with high-grade glioblastoma.

Galectin-1 in ovarian cancer

Increased expression of gal-1 in human ovarian carcinoma cells and preferential accumulation of gal-1 in cancer-associated stroma suggests its role in the cross-talk between cancer cells and the associated stroma culminating in a change in behaviour of the cancer cells. Higher Gal-1 expression is closely associated with higher histological grade, more lymph node metastases and a more advanced FIGO stage. Targeting Gal-1 in ovarian cancer may serve as a promising treatment and may function as a molecular biomarker in predicting metastasis and prognosis in ovarian cancer. There has been a tremendous demand for the identification of useful markers for the progression of ovarian cancers since quite a few ovarian cancers are negative for the CA-125 marker that is also very less specific and sensitive. Galectin-1 has emerged as a protein commonly elevated in ovarian cancer. Serum galectin-1 levels were found to be significantly higher in patients with metastatic disease compared with patients with localized tumors. It has been shown that a combination of CA-125

and Galectin-1 serves as a possible two-marker combination. A study has shown that Galectin-1 expression in stroma would serve as an independent prognostic marker. A recent study showed that galectin-1 serum levels in ovarian cancer patients might serve as a better surrogate biomarker in early detection of the disease, monitoring treatment response and as the indicator of tumour invasion and metastasis. The study also compared the diagnostic efficacy of Galectin-1 and CA125, used currently in the detection of the disease, and found that Galectin-1 had greater discriminative ability than CA125 levels between healthy controls and ovarian cancer patients.

Galectin-1 in cervical cancer

In cervical cancer, galectin-1 expression was higher and Immunohistochemical studies detected increased galectin-1 expression in intracellular tumor (nuclei and cytoplasm) portion, peritumoral stromal portion and an extracellular stromal portion or in fibrocytes and fibroblasts in the stroma of cervical cancer. Conversely, these studies had shown negative or absent expression of galectin-1 in normal cervical tissue samples. Two recent studies in cervical cancer showed a positive correlation between galectin-1 expression and tumor stage, tumor invasion and lymph node metastasis. It had been predicted that changes in the levels of galectin-1 might determine the prognosis of cervical cancer. The 5-year progression-free survival PFS for patients with low galectin-1 expression was 84%, whereas for high galectin-1, expression was 73.2%. In another study, the receiver operating characteristics curve analysis indicated a better predictive ability of galectin-1 expression in specimens of cervical squamous cell carcinoma (SCC, stage I-II, after radiation therapy) for local recurrence (LR) and cancer-specific survival (CSS) than stromal expression. Studies have shown that Gal-1 is an independent prognostic factor in stage I-II cervical cancer patients undergoing definitive radiation therapy.

Galectin-1 in classical Hodgkin lymphoma

Gal-1 has been implicated as a modulator of classical Hodgkin lymphoma (cHL). Expression of this protein by Reed Sternberg cells has been demonstrated to confer an immune privilege to cHL cells, creating an appropriate niche for tumor progression which contributes to poorer prognosis in cHL patients, which further supports the hypothesis identifying Gal-1 as a potential novel biomarker that may be useful in the prognostic and predictive analysis

of cHL.

Galectin-1 in head and neck cancer

The increased secretion and expression of galectin-1 could be used for the prognosis of patients with head and neck cancer. Galectin-1 participates in carcinogenesis and tumor progression by stimulating cancer cell proliferation and survival, migration, invasion, and angiogenesis, as well as immune system escape through multiple mechanisms. The most recent studies revealed that galectins might be used as markers for prognosis in head and neck cancer. In squamous cell carcinomas of head and neck, upregulation of galectin-1 presence significantly correlated to the presence of smooth muscle actin-positive cancer-associated fibroblasts in the tumor, which are an indicator of poor prognosis.

Galectin-1 in renal cell carcinoma

Studies have suggested that Gal-1 could be a potential marker for Renal Cell Carcinoma (RCC). The molecular mechanisms of Galectin-1 in RCC remain unknown. Still, the studies have evaluated the contribution of Gal-1 in clinical relevance to kidney cancer pathogenesis, where Gal-1 was markedly upregulated in kidney cancer cell lines and tissue specimens. Knockdown of Gal-1 significantly reduced epithelial-mesenchymal transition (EMT), clonogenicity, and invasiveness of kidney cancer cells. Gal-1 silencing repressed angiogenesis-inducing activities of RCC cells both in vitro and in vivo. In addition, concomitant overexpression of Gal-1 could predict a poorer survival rate in patients with RCC.

Galectin-1 in colon cancer

Studies in colon cancers indicated significantly higher levels of galectin-1 in poorly differentiated and invasive tumours compared to differentiated tumours or normal adjacent tissue. Neoplastic perineural invasion is one of the metastatic spreading routes, and is reported that perineural invasion is an important characteristic of various malignancies, including CRC. Serum Galectin-1 concentrations positively correlated with parameters of malignancy, including perineural invasion, lymph node involvement and distant metastases. Higher expression of peritumoral Galectin-1 was associated with both presence of perineural invasion and poor differentiation of colorectal carcinoma.

Concluding Remarks

Galectin-1 serves a fundamental role in the progression of

cancer by altering tumor microenvironment, angiogenesis, promoting metastasis and modulating immune response. The available data demonstrate a potential role for galectin-1 as a predictive biomarker in various cancers. However, further research is required in understanding these versatile proteins and how they can be exploited for diagnostic, prognostic and even therapeutic purposes in cancer patients.

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