

Galectins in cancer: carcinogenesis, diagnosis and therapy

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Abstract: A major breakthrough in the field of medical oncology has been the discovery of galectins and their role in cancer development, progression and metastasis. In this review article we have condensed the results of a number of studies published over the past decade in an effort to shed some light on the unique role played by the galectin family of proteins in neoplasia, and how this knowledge may alter the approach to cancer diagnosis as well as therapy in the future. In this review we have also emphasized the potential use of galectin inhibitors or modulators in the treatment of cancer and how this novel treatment modality may affect patient outcomes in the future. Based on current pre-clinical models we believe the use of galectin inhibitors/modulators will play a significant role in cancer treatment in the future. Early clinical studies are underway to evaluate the utility of these promising agents in cancer patients.

Keywords: Cancer; solid tumors; lectins; galectins

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Introduction

Galectins are a group of proteins known for their ability to bind to B-galactoside sugars, either by N-linked or O-linked glycosylation (1,2). Galectins were first isolated from chick muscle and calf heart and lungs in 1976. Since then, galectins have been named in the order of discovery with as 15 members of the family identified so far. Each galectin has a carbohydrate recognition domain (CRD), and are classified according to the number and structure of these CRD (1,2). Galectins are therefore divided into tandem, dimeric and chimeric galectins (*Figure 1*). Dimeric galectins have two identical CRD subunits, tandem ones have two distinct CRD subunits and chimeric ones have one or even multiple subunits of the same type (1,2). Galectins-1, -2, -5, -7, -10, -11, -13, -14 and -15 are all dimeric galectins with

galectins-4, -5, -8, -9 and -12 falling under the tandem category (1,2). Galectin-3 is the only chimeric galectin discovered in mammals thus far (1,2). In terms of species distribution, galectin-1 (Gal-1), -2, -3, -4, -7, -8, -9, -10, -12 and -13 are present in humans, galectin-5 and -6 in rodents and galectin-11, -14 and -15 were isolated from sheep and goats.

Carcinogenesis, tumor growth and progression are complex and multifactorial processes that depend on an interplay between genotoxic insults, external cellular pressures, tissue micro-environment, and the functionality and modulation of innate cellular repair mechanisms and the body's immune system. Since their discovery, galectins have been implicated in the development of cancer, the pathogenesis of heart failure and ventricular remodeling, infectious processes, such as HIV, and various other

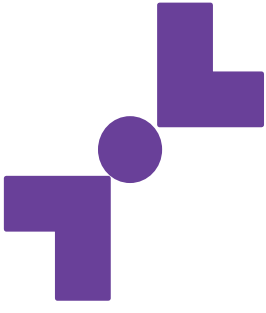
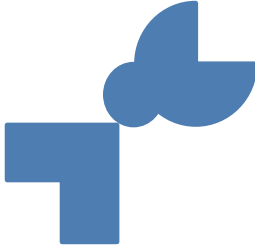

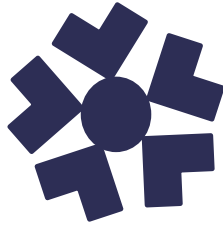
Dimeric (2 identical CRDs)	Tandem (2 distinct CRDs)	Chimeric (one or multiple CRDs)
1, 2, 5, 7, 10, 11, 13, 14, 15	4, 5, 8, 9, 12	3
		 or 

Figure 1 Structure and classification of galectins.

autoimmune and inflammatory processes. Over the past decade the role of galectins in various malignancies has been extensively studied, with the most commonly examined being galectins-3 and -1, followed by -7, -9 and -4. The observation that galectins may have different functions in different tumors adds an additional layer of complexity to their study. For this reason, it is necessary to examine and discuss their potential role in specific neoplasms, separately.

The reproductive system

Galectins in breast cancer

Galectins appear to play an important role in breast cancer progression and metastasis. In a study examining the role of Gal-1 in breast cancer models, investigators found that the frequency of Gal-1 expressing cells in human breast cancer biopsies correlated positively with tumor grade, while specimens from patients with benign hyperplasia showed negative or limited Gal-1 staining (3). Silencing Gal-1 expression in the 4T murine mammary tumor induced a marked reduction in both tumor growth and the number of lung metastasis. Gal-1 attenuation in 4T 1 cells also reduced the frequency of CD4+, CD25+, Foxp3+ T-cells within the tumor draining lymph nodes, spleen and lung metastases (3). Simone and her group studied the function of Gal-3 as a molecular signature of tumors, and showed that Gal-3 B-galactoside binding lectin, coats membranes of most cancer cells and is involved in metastasis, endothelial recognition and evasion of immune surveillance through the killing of activated T cells (4). As early as 2005, Gal-9 was

reported to be a good prognostic factor, related to its anti-metastatic potential in breast cancer (5). Gal-7 was initially described as a marker of epithelial differentiation expressed in the stratified epithelium of various tissues (6). In breast cancer Gal-7 expression is significantly augmented in aggressive molecular subtypes, notably in estrogen receptor negative tumors and in cell lines with a basal like phenotype (7). Studies using mouse models have further demonstrated that high expression of Gal-7 was sufficient to increase the metastatic potential of breast cancer cells, rendering them more resistant to apoptosis (7). It has also been shown that p53-induced Gal-7 expression in breast cancer cells correlates with increased NF- κ B activity, indicating Gal-7 induction by mutant p53 is dependent on NF- κ B activity. In this study NF- κ B was found to bind endogenous Gal-7 promoter suggesting Gal-7 could be part of the common pathway used by mutant p53 to promote cancer progression (7). Finally, overexpression of Gal-7 has been shown to enhance spontaneous metastasis of breast cancer cells, especially high grade breast carcinomas, including HER-2 overexpressing and basal like groups (8). In HER-2 overexpressing cases, Gal-7 expression was associated with lymph node axillary metastasis (8).

Galectins in prostate cancer

Gal-1 is the most abundantly expressed galectin in prostate cancer tissue and is markedly upregulated during disease progression (9). In contrast, all other galectins were expressed at lower levels or downregulated during disease evolution, while expression of Gal-8 was unchanged (9). In

the same study, Gal-1 expression in human prostate cancer tissue arrays correlated with the presence of angiogenesis, particularly in advanced stages of the disease (9). Silencing Gal-1 expression in prostate cancer cells reduced tumor vascularization without altering expression of other angiogenesis-related genes. In contrast to other cancers, Gal-3 is down regulated in prostate cancer (9). However, Gal-3 molecular cleavage appears to occur during disease progression with higher levels of cleaved Gal-3 correlating with metastatic disease (10). Gal-3 knockdown using small interfering RNA (siRNA) has been associated with reduced cell migration, invasion, cell proliferation, anchorage-independent colony formation, and tumor growth in nude mice (10). Gal-3 knockdown in human prostate cancer PC3 cells has led to cell-cycle arrest at G₁ phase, up-regulation of nuclear p21, and hypophosphorylation of the retinoblastoma tumor suppressor protein (pRb), with no effect on cyclin D1, cyclin E, cyclin-dependent kinases (CDK2 and CDK4), and p27 protein expression levels. Raz and coworkers have demonstrated that cleavage of Gal-3 by matrix metalloproteinases (MMP)-2/-9 is associated with angiogenesis, growth and resistance to apoptosis in mouse models of breast and prostate cancers (9,11). Lastly, Knapp *et al.* have reported the presence of a Gal-3 expression gradient in prostate cancer and benign prostate tissues suggesting Gal-3 expression may be useful in predicting biochemical recurrence (11).

Galectins in cervical cancer

Gal-1 expression has been shown to correlate with the depth of invasion of cervical cancer and the extent of lymph node metastasis (12). Similarly, downregulation of Gal-1 caused a decline in cell growth, proliferation and invasive (12). Huang *et al.* have shown that Gal-1 mediates radioresistance in cervical cancer cell lines through the H-Ras-dependent pathway involved in DNA damage repair (13). This same group concluded that Gal-1 is an independent prognostic factor in stage I-II cervical cancer patients undergoing definitive radiation therapy (14). In contrast to Gal-1, elevated Gal-7 levels seem to be associated with improved outcomes after definitive radiation therapy in patients with cervical cancer while Gal-9 is inversely associated with cell differentiation and malignant potential of cervical cancer cells (15,16).

Galectins in other cancers of the reproductive system

A correlation between Gal-1 expression and the histopathological

grade of vulvar tissues has been suggested, implicating this molecule in the progression of vulvar neoplasia (17).

The respiratory system

Galectins in lung cancer

Various studies have been conducted on the effect of galectins in the pathogenesis, aggression and response to treatment in lung cancer, with Gal-1 being the most investigated. Kuo *et al.* evaluated the role of Gal-1 in murine lung cancer microenvironment and showed that tumor-derived Gal-1 secretion was associated with tumor-associated dendritic cells (TADCs) production of heparin-binding EGF (HB-EGF)—like growth factor, resulting in tumor progression (18). The association of Gal-1 with integrin $\alpha 6\beta 4$ and Notch1/Jagged2 results in enhanced invasion and migration of lung cancer cells and silencing Gal-1 decreased invasion, migration as well as increase sensitivity to chemotherapy (19,20). Indeed, 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 worse prognosis (21,22). Gal-4 has also been shown to correlate with lymph node metastasis and adverse survival outcomes in lung adenocarcinoma, especially the acinar predominant type (23). Along with histopathological analysis Gal-4 serves as a strong predictor for metastatic potential in this tumor type (23).

The digestive system

Galectins in esophageal and gastric cancers

Gal-7 has been found to be highly expressed in esophageal squamous cell cancers, possibly serving as a biomarker for this disease (24). Gal-7 is also significantly down regulated in gastric cancer cells, suggesting it might play a suppressive role in this neoplasm (25). In contrast, Gal-3 enhances gastric cancer cell motility, possibly by up regulating fascin-1, an actin-binding protein mediating metastatic of the tumor (26).

Galectins in colon cancer

In colon cancer Gal-3 plays an important role in potentiating cell migration and metastasis through activation of certain kinase pathways like the K-Ras-Raf-Erk1/2 pathway (27). Galectins-2, -4, and -8 may also enhance metastasis in colon cancer cells by mediating

endothelial cell adhesion (28).

Galectins in pancreatic cancer

With regards to progression of pancreatic cancer, Song *et al.* has proposed that Gal-3 plays an important role in pancreatic cancer metastasis through activation of Ras, ERK, AKT and Rel A pathways, hence enhancing cell migration and survival (29). Interestingly, Gal-4 may function as a cell-to-cell surface adhesion molecule in pancreatic cancer, preventing pancreatic cell detachment (30).

The nervous system

Galectins in brain tumors

Galectins-1, -3, -4, and -8 have been shown to play a role in the progression of brain gliomas. Gal-1 appears to play a role in augmenting myeloid-derived suppressive cell (MDSC) accumulation and angiogenesis within the glioma microenvironment (31). Silencing Gal-1 expression in their models resulted in prolonged survival, as well as decreased infiltration of the brain with myeloid derived suppressor cells (31). The effect of Gal-1 with regards to response to the chemotherapy agent temozolomide has also been studied. Interestingly, Gal-1 expression was associated with increased transcription of the genes causing temozolomide resistance, thereby suggesting the possibility of interfering with Gal-1 expression as a strategy to modulate temozolomide resistance in brain tumors (32). Gal-3 is abundantly expressed in malignant gliomas, and studies suggest it is found in early preneoplastic lesions. Different from findings in earlier glial lesions, Gal-3 has been shown to be expressed in both neoplastic astrocytes cells and microglia of malignant glioma, suggesting Gal-3 is activated in microglia and macrophages according to disease progression (33).

The skin

Galectins in melanoma

Melanoma is one of the most aggressive cancers, with a very high mortality rate. Gal-3 has been found to play a role in the growth and progression of melanomas. Gal-3 seems to act by modulating the expression of the transcription factor NFAT1 (NFATC2) and regulating autotaxin expression at the transcriptional level (34). Autotaxin stimulates angiogenesis, tumor growth, and metastasis *in vivo* and silencing Gal-3 results in decreased NFAT1, autotaxin expression and tumor

growth (34). Gal-1 expression by tumor and endothelial cells seems to play a role in the resistance of melanoma cells to radiotherapy and chemotherapy through direct modulation of angiogenesis, as well as the immunosuppressive cells in the tumor microenvironment (35,36). Therefore, targeting Gal-1 may represent a potential therapeutic strategy against melanomas (36).

The kidneys

Galectins in renal cell cancers

Gal-3 has been found to be overexpressed in clear cell renal cell carcinoma (CCRCC), compared to normal tissue, with a significantly higher expression in metastatic disease (37,38). Other studies have suggested a protective role for Gal-3 in renal carcinoma cells against apoptosis, as knockdown of Gal-3 expression rendered resistant cells sensitive to arsenic trioxide (39). Gal-3 was found to inhibit ATO-induced apoptosis through enhancing Bcl-2 expression and stabilizing mitochondria (39). This finding implicates Gal-3 in the resistance of renal carcinoma cells to cytotoxic treatment. Gal-1 has been shown to promote tumor progression through upregulation of CXCR4 via NFkB, as evidenced in studies of Gal-1 knockdown in renal carcinoma cells (40). These investigators also found that Gal-1 was overexpressed in renal carcinoma cell lines and in samples from patients with metastasis (40). Knockdown of Gal-1 gene expression in renal cancer cell lines reduced cell invasion, clonogenic ability, and epithelial-mesenchymal transition *in vitro*, reduced tumor outgrowth *in vivo* and inhibited the angiogenesis-inducing activity of these cells both *in vitro* and *in vivo* (40).

Galectins in bladder cancer

Gal-3 is also highly expressed in both transitional cell and squamous cell carcinomas of the bladder, with higher levels detected in high grade tumors compared to low grade ones (41). Other studies have also confirmed the expression of Gal-1 in bladder cancers and correlated it with tumor grade and metastasis (42).

The endocrine system

Galectins in pituitary tumors

In the case of pituitary tumors Gal-3 seems to be specifically expressed in lactotroph and corticotroph cells, with inhibition of Gal-3 resulting in apoptosis and decreased cell proliferation (43).

Galectins in thyroid and parathyroid cancers

Gal-3 has been shown to be preferentially expressed in malignant thyroid tissue compared to benign thyroid hyperplasia and normal glands (44). A retrospective analysis of Gal-3 and thyroid peroxidase (TP) levels in thyroid cancers demonstrated both Gal-3 and TP are specifically expressed in papillary thyroid carcinoma suggesting these may serve as a diagnostic and prognostic indicator in patients with this histological sub-type (45). Gal-3 overrides the tumor suppressor activity of caveolin-1 (Cav-1) and functions in concert with Cav-1 to promote focal adhesion turnover and tumor cell migration and invasion (46). Thus it appears that Gal-3 and Cav-1 function synergistically to promote focal adhesion signaling, migration and progression of differentiated thyroid cancer (46). Similarly, Gal-3 has been associated with the diagnosis of highly proliferative tumors of the parathyroid gland (47).

Galectins in adrenal tumors

Gal-3, nm23 and COX-2 expression has been reported to be useful in differentiating between malignant and benign pheochromocytomas (48). The combined expression of Gal-3 and COX-2 has been associated with malignant lesions, whereas nm23 expression in the absence of Gal-3 and COX-2 expression indicates a more benign histology (48).

Conclusions: implications of galectin expression and cancer

As discussed, galectins serve a fundamental role in the progression of cancer by altering tumor microenvironment, angiogenesis, metastatic potential and modulating immune response (*Table 1*). The available data indicate a potential role for galectin inhibitors in the treatment of cancer. The cellular

Table 1 Summary of the effect of galectins on specific cancers

Galectin	Effect on cancer
Galectin-1	Breast: enhances tumor growth and metastasis and suppresses T cell function Prostate: upregulates angiogenesis Cervical: promotes progression, radioresistance Lung: enhances tumor progression, invasion and migration by increasing HB-EGF and by altering tumor milieu Gastric: promotes progression Kaposi: promotes angiogenesis Melanoma: modulates tumor environment by altering T cells , causes resistance of melanoma cells to cytotoxic stimuli and enhances angiogenesis Renal cell cancer: increase tumor progression and angiogenesis Bladder cancer: increase in tumor grade and metastasis Glioma: myeloid cell accumulation within high grade gliomas
Galectin-3	Breast: helps evade immune surveillance and killing of active T cells Prostate: cleavage during malignant transformation and progression of prostate cancer Cervical: resistance to chemotherapy Sex cord tumors: tumor specific role—increased in leydig cell cancer, decreased in Sertoli cell cancer, increased in non seminomas, decreased in seminomas Lung: increased expression in NSCLC Gastric: enhances gastric cell motility and mediates metastasis Melanoma: increased growth, progression, angiogenesis and metastasis Renal cell cancer: antiapoptotic, resistance to cytotoxic treatment Bladder: increases malignant potential Pituitary: increased expression Thyroid: increased progression of differentiated thyroid cancer Pheochromocytoma: predicts benign vs. malignant potential Glioma: activated in microglia and macrophages the glioma progresses
Galectin-7	Breast: increased metastatic potential and resistance to apoptosis Cervical: curative role, improved outcome after definitive radiotherapy Esophageal: highly expressed in squamous cell cancer Gastric: suppressive role
Galectin-4	Lung: increases metastatic potential of ancinar predominant types of adenocarcinoma Pancreatic: acts on the cell surface as an adhesion molecule and prevents release of pancreatic cancer cells
Galectin-9	Breast: antimetastatic, inversely associated with malignant potential
Galectins-2 & 8	Colon: enhance metastasis be mediating adhesion to endothelial cells

effects of Gal-1 and -3 are the most extensively studied and small molecule inhibitors are currently being developed. Importantly, Gal-9 expression has been shown to naturally hinder cancer progression and the development of Gal-9 agonists may offer additional therapeutic opportunities for cancer patients. Additional studies are underway to develop effective pharmacologic inhibitors and agonists of specific galectins and determine their role in cancer care.

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