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Maria C Vladoiu, Marilyne Labrie, Yves St-Pierre

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Intracellular galectins in cancer cells: Potential new targets for therapy (Review)

MARIA C. VLADOIU, MARILYNE LABRIE and YVES ST-PIERRE

INRS-Institut Armand-Frappier, Laval, QC H7V 1B7, Canada

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Abstract. Dysregulation of galectin expression is frequently observed in cancer tissues. Such an abnormal expression pattern often correlates with aggressiveness and relapse in many types of cancer. Because galectins have the ability to modulate functions that are important for cell survival, migration and metastasis, they also represent attractive targets for cancer therapy. This has been well-exploited for extracellular galectins, which bind glycoconjugates expressed on the surface of cancer cells. Although the existence of intracellular functions of galectins has been known for many years, an increasing number of studies indicate that these proteins can also alter tumor progression through their interaction with intracellular ligands. In fact, in some instances, the interactions of galectins with their intracellular ligands seem to occur independently of their carbohydrate recognition domain. Such findings call for a change in the basic assumptions, or paradigms, concerning the activity of galectins in cancer and may force us to revisit our strategies to develop galectin antagonists for the treatment of cancer.

Contents

1. Introduction

Galectins represent a family of evolutionarily conserved animal lectins that are widely distributed from lower invertebrates to higher vertebrates. They were initially described in the electric eel, *Electrophorus electricus*, as low molecular weight, β-galactoside binding proteins (1). Since then, galectins have been numbered according to the order of their discovery. The 15 family members are now classified according to their structure and number of carbohydrate recognition domain (CRD). The prototype subfamily of galectins (galectin-1, -2, -5, -7, -10, -11, -13, -14 and -15) consists of a single CRD with a short N-terminal sequence. The tandem-repeat type subfamily (galectin-4, -6, -8, -9 and -12) has two non-identical CRDs joined by a short linker peptide sequence. There is also a chimerical form of galectin (galectin-3) that contains one CRD connected to a non-lectin domain.

One of the first clues that galectins were involved in cancer was published more than 25 years ago when it was observed that they were differently regulated in normal and cancer tissues. Since then, a large number of studies have focused on the role of galectins in cancer and excellent reviews on the role of galectins have been published (2-5). Historically, studies on the role of galectins in cancer have mostly focused on their ability to bind membrane-anchored cell surface receptors via their CRD. Their dimeric form (or multimeric in the case of galectin-3) induces crosslinking of the receptors and formation of a lattice that triggers a cascade of transmembrane signaling events. For example, binding of galectin-3 protects EGF and TGF-β receptors from negative regulation via constitutive endocytosis and increases sensitivity of tumor cells to growth factors (6). Binding to cell surface receptors can also induce apoptosis. This is particularly relevant in the case of galectin-1, which is capable of inducing apoptosis of T-cells and potentially create an immunosuppressive tumor microenvironment (7). Alternatively, binding to cell surface receptors can facilitate intercellular adhesion (to promote homo- and heterotypic aggregation) or adhesion of tumor cells to extracellular matrix proteins. Exhaustive efforts have thus been deployed for the identification of highly selective and potent galectin inhibitors. Despite decades of research, the progression in this field has been relatively slow. In most cases, these inhibitors are peptides or high molecular weight, naturally occurring polysaccharides that are used to specifically block the binding of extracellular galectins to carbohydrate structures on cell surface receptors. While targeting extracellular galectins is warranted, such inhibitors are largely if not completely ineffective at targeting intracellular galectins. Indeed, most galectins preferentially exist in intracellular

Correspondence to: Professor Yves St-Pierre, INRS-Institut Armand-Frappier, University of Quebec, 531 Boul. Des Prairies, Laval, QC H7V 1B7, Canada
E-mail: yves.st-pierre@iaf.inrs.ca

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compartments, consistent with the fact that they do not harbor a signal sequence and are transported outside the cells via a non-classical secretory pathway, possibly via galectin-rich vesicles or exosomes. A better understanding of their intracellular functions in cancer cells is thus critical to help develop new anticancer therapies directed at these proteins.

2. Where do we find galectins inside the cells?

The answer to this question is rather simple: almost anywhere (Fig. 1). They can be detected in various intracellular compartments of both normal and cancerous cells. Frequently, modifications in the subcellular localization occur when cells undergo cell-transformation into malignant phenotypes (4). It is noteworthy to mention that galectins expression is also modulated during some of these cell transformation processes, hence their presence/absence in those subcellular localizations is not exclusive to protein translocation (8). Up to now, however, our knowledge of intracellular galectins has mostly been obtained while studying galectin-3. As we gain more and more knowledge on other members of the galectin family, we find overwhelming evidence that most if not all galectins are often expressed inside the cells. Here we describe the intracellular localization of various galectins with their respective cancer tissues and/or cell lines (Table I).

Galectin-1 is observed in the nuclear compartment of transfected HeLa cells (9) and the inner plasma membrane of colorectal adenocarcinoma cells (HCT116) (10). Moreover, its presence is also seen in the cytosol of neuroblastoma and small cell lung carcinoma tissues, testicular interstitial and cervical carcinoma cell lines (MA-10 and HeLa), hypopharyngeal (HSCCs) and laryngeal (LSCCs) squamous cell carcinoma tissues, human melanoma cell lines (A375 and A2058) and colorectal cancer tissues including adenomas, carcinomas and metastases from patients (9,11-15). Although fewer studies have been conducted on galectin-2, the available data indicate its presence in the nucleus of genetically engineered human colon cancer cells that have ectopic stable expression (16) in addition to gastric carcinoma tissues, epidermoid carcinoma, osteosarcoma and glioblastoma cell lines (A-431, U-2 OS and U-251MG) (17,18). Its presence has also been reported in the cytosol of gastric carcinoma tissues and in mitochondria of epidermoid carcinoma, osteosarcoma and glioblastoma cell lines (A-431, U-2 OS and U-251MG) (17,18). In the case of galectin-3, one of the most investigated members of the galectin family, its presence is detected in the nucleus of aggressive endometrial adenocarcinoma, melanoma cell lines, malignant thyroid carcinomas (follicular adenoma, Hürthle cell adenoma and papillary carcinoma) (19-21). Galectin-3 is also found in the cytosol of colonic adenomas/carcinomas tissues, follicular/papillary thyroid carcinomas, endometrial adenocarcinoma, human melanoma cell lines (MlDo and M4Be), malignant thyroid carcinoma (follicular adenoma, Hürthle cell adenoma and papillary carcinoma) and in tongue squamous cell carcinoma tissues (19-24). Additionally, galectin-3 is found in the mitochondria of colorectal adenocarcinoma cell line (SNU-769B), in endosomal compartments of breast adenocarcinoma cell line (SKBR3), and in apical membrane regions of human colon adenocarcinoma cell lines (T84 and HCT116) (10,25-27). Galectin-4 is detected in the cytosol of human breast ductal carcinoma tissues (28,29) and pancreatic adenocarcinoma cell line (Pa-Tu-8988S) (29) as well as inside the basal plasma membrane of human colon adenocarcinoma cells (T84) (27). Galectin-7, which has recently attracted more interest in cancer because its preferential expression in epithelial tissues and carcinomas, is seen in the nucleus of many cancer cells, including hypopharyngeal (HSCCs) and laryngeal (LSCCs) squamous cell carcinomas tissues, colon carcinoma cells (DLD-1), cervical adenocarcinoma (HeLa), epithelial ovarian cancer tissues and oral epithelial dysplasia tissues (13,30-32). Galectin-7 is also observed in the cytosol of the colon carcinoma cell line DLD-1, cervical adenocarcinoma cells (HeLa), epithelial ovarian cancer and oral epithelial dysplasia tissues (17,30-32). Like galectin-3, it is also detected in mitochondrial fractions, most notably in the case of human colorectal carcinoma and cervical adenocarcinoma cell lines (HCT116, HeLa) and the HaCaT keratinocyte cell line (33). Galectin-8 expression is detected in the cytosol, nucleus and mitochondria of tumor-associated epithelial cells from human prostate and breast tissues (34). Intracellular galectin-9 is observed in the cytosol of human melanoma cell lines (MM-BP and MM-RU) and the MCF-7 breast carcinoma cell line (35,36). Galectin-10 is observed in the nuclei and cytosol of epidermoid carcinoma cells and in the cytoplasmic compartments of glioblastoma and osteosarcoma. In the human promyelocytic leukemia HL-60 cell line, it is found in the nucleus, cytosol and mitochondria (37) while its localization is associated with the inner plasma membrane of many glioblastoma cell lines (A-431, U-2 OS and U-251MG) (17). Galectin-12 is observed in the cytosol and mitochondria of osteosarcoma and glioblastoma cell lines (U-2 OS and U-251MG) (17).

Although there are no reports yet that other galectins are present inside cancer cells, there are indications that this may well be the case given their presence inside normal cells. For example, galectin-12, a close structural homolog of galectin-7, has been found in the nucleus and mitochondrial fractions of adipocytes (38-40). The fact that galectin-12-deficient mice have abnormal mitochondrial activity is particularly interesting considering the key role of mitochondria in energy metabolism of cancer cells (41,42). Galectin-10 is also found inside human regulatory T-cells and other inflammatory cells (43) while galectin-13 is found in the perinuclear area of syncytiotrophoblasts (44). Computational predictions of where galectins resides in a cell show that it is logical to assume that many galectins will be present within several intracellular compartments. For example, using pSORT, a commonly used tool to predict intracellular localization of proteins, we found that all galectins have a strong preference for cytoplasmic, nuclear and mitochondrial compartments (Table II) (45,46). We have obtained similar results using other computational tools (unpublished data).

3. Intracellular functions of galectins in cancer

The main challenge in studying the galectin functions in neoplasms remains their opposing functions in tumor progression. Depending on the type of cancer, one galectin

Table I. Intracellular localization of galectins in different cancers.

Localization	Galectin	Cancer cell line/tissue from patients	(Refs.)
Nuclear	Galectin-1	Cervical adenocarcinoma	(9)
	Galectin-2	Colorectal carcinoma	(16)
		Epidermoid carcinoma, osteosarcoma and glioblastoma	(17)
		Gastric carcinoma	(18)
	Galectin-3	Adenocarcinoma of the endometrium	(19)
		Melanoma	(20)
		Thyroid carcinoma (follicular/Hürthle cell/papillary)	(21)
	Galectin-7	Hypopharyngeal/laryngeal squamous cell carcinoma	(13)
		Colorectal carcinoma and cervical adenocarcinoma	(30)
		Epithelial ovarian cancer	(31)
		Oral epithelial dysplasia	(32)
	Galectin-8	Tumor-associated epithelial cells from prostate and breast carcinoma	(34)
	Galectin-10	Epidermoid carcinoma	(17)
		Human promyelocytic leukemia (HL-60)	(37)
Cytoplasmic	Galectin-1	Cervical adenocarcinoma	(9)
		Neuroblastoma and small cell lung carcinoma	(11)
		Testicular (interstitial cell) carcinoma	(12)
		Hypopharyngeal/laryngeal squamous cell carcinoma	(13)
		Melanoma	(14)
		Colorectal carcinoma	(15)
	Galectin-2	Gastric carcinoma	(18)
	Galectin-3	Colorectal adenoma and carcinoma	(22)
		Follicular and papillary thyroid carcinoma	(23)
		Adenocarcinoma of the endometrium	(19)
		Melanoma	(20)
		Thyroid carcinoma (follicular/ Hürthle cell/papillary)	(21)
		Squamous cell carcinoma of the tongue	(24)
	Galectin-4	Ductal breast carcinoma	(28)
		Pancreatic adenocarcinoma	(29)
	Galectin-7	Colon carcinoma and cervical adenocarcinoma	(30)
		Epithelial ovarian cancer	(31)
		Epidermoid carcinoma and osteosarcoma	(17)
		Oral epithelial dysplasia	(32)
	Galectin-8	Tumor-associated epithelial cell from prostate and breast carcinoma	(34)
	Galectin-9	Melanoma	(35)
		Breast carcinoma	(36)
	Galectin-10	Epidermoid carcinoma and glioblastoma	(17)
		Human promyelocytic leukemia (HL-60)	(37)
	Galectin-12	Osteosarcoma and glioblastoma	(17)
Mitochondrial	Galectin-2	Epidermoid carcinoma, osteosarcoma and glioblastoma	(17)
	Galectin-3	Colorectal adenocarcinoma	(25)
	Galectin-7	Colorectal carcinoma and cervical adenocarcinoma	(33)
	Galectin-8	Tumor-associated epithelial cell from prostate and breast carcinoma	(34)
	Galectin-10	Human promyelocytic leukemia (HL-60)	(37)
	Galectin-12	Osteosarcoma and glioblastoma	(17)
Endosomal compartments	Galectin-3	Breast adenocarcinoma	(26)
Plasma membrane	Galectin-1	Colorectal adenocarcinoma	(10)
	Galectin-3	Colorectal adenocarcinoma	(10,27)
	Galectin-4	Colorectal adenocarcinoma	(27)
	Galectin-10	Epidermoid carcinoma, osteosarcoma and glioblastoma	(17)

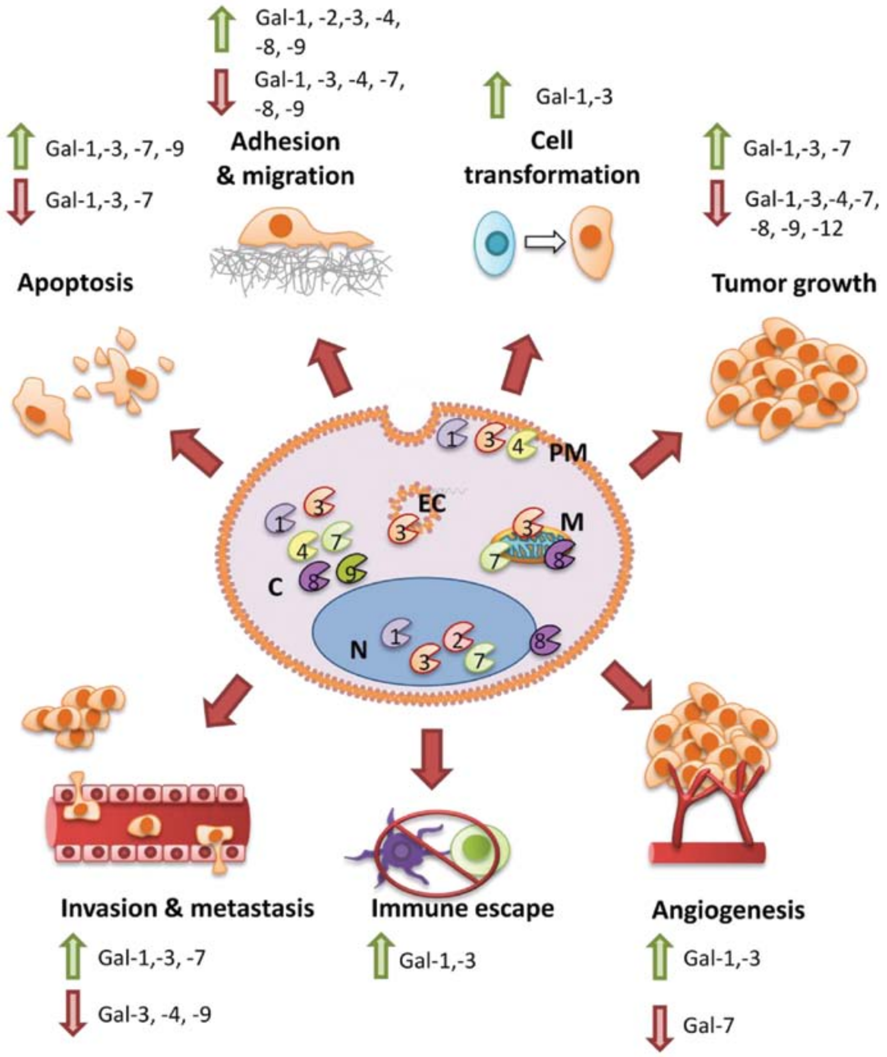

Figure 1. Pro- and anti-tumoral functions of galectins in cancer. Galectins are found in the cytoplasm (C), mitochondria (M), nucleus (N), endosomal compartments (EC) and inner plasma membrane (PM). They are capable of modulating many aspects of tumor progression such as cell adhesion and migration, immune escape, cell transformation, apoptosis, angiogenesis, tumor growth, invasion and metastasis.

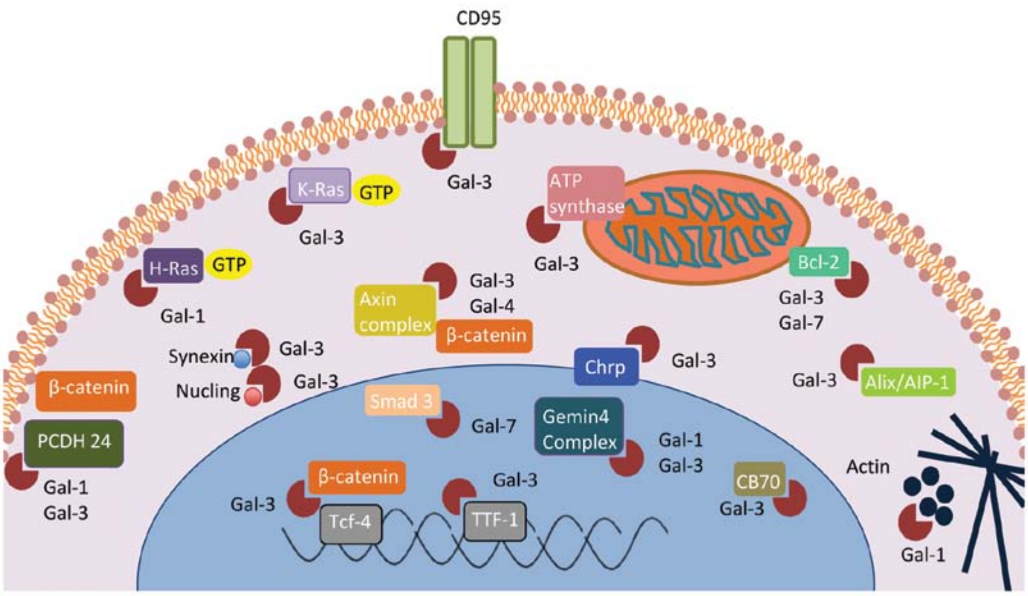

Figure 2. Intracellular binding partners of various galectins. Galectins have numerous binding partners with respect to their inner compartmentalization.

Table II. Predicted intracellular localization of galectins.

Cellular compartment	Galectin (%) 1	2	3	4	7	8	9	10	12	13
Cytoplasmic	65	52	26	65	65	70	65	52	39	61
Nuclear	22	26	48	17	17	17	17	13	13	17
Mitochondrial	4	9	9	13	17	9	4	4.3	44	13
ER	4	-	-	-	-	4	4	-	-	4
VSS	4	-	-	4	-	-	4	-	-	-
Vacuolar	-	4	-	-	-	-	-	-	-	4
Cytoskeletal	-	4	-	-	-	-	-	22	4.3	-
Peroxisomal	-	4	-	-	-	-	-	9	-	-

ER, endoplasmic reticulum; VSS, vesicles of secretory system.

can either have pro/antitumoral properties (5,47,48) (Fig. 1). This characteristic of galectins can be explained by the large diversity of binding partners (Fig. 2) and by the expression pattern of these partners, which varies contingent to the cell type. Another proposed hypothesis supporting the dual functionalities of galectins in cancer is based on the distinct compartmentalization of the proteins within the cells. In fact, it was shown that intracellular localization of galectins differs according to the cell type and tumor progression stage. Supporting this hypothesis, Califice *et al* (47) demonstrated that overexpression of galectin-3 in LnCap prostate cancer cells in the cytoplasm induces invasion behavior, anchorage-independant growth, tumor growth and angiogenesis and reduces apoptosis, while nuclear overexpression results in the opposite biological activities. Hence, it is of great interest to take a closer look at the intracellular localization of these galectins and the impact it has on their biological functions with regards to cancer progression. Here, we discuss the main findings on the possible roles of intracellular galectins in cancer. A detailed report of their functions and their putative ligands is found in Tables III and IV.

Cell transformation. A positive correlation between the expression of galectin-1 and -3 and malignant transformation has been established using different cellular models (49-51). Although the mechanisms involved are not completely clear, it potentially involves interactions with membrane-bound H-Ras and K-Ras (52-54). Interestingly, Ras-transformed NIH-3T3 cells have increased expression of galectin-1 and galectin-3 compared to control cells (55). This induction is not necessarily a consequence of Ras pathway activation but rather a secondary effect of cell transformation. Hebert *et al* demonstrated that Ras transfected cells that have a transformed phenotype, express galectin-3 while Ras transfected cells that have not achieved cell transformation do not (56). Another possibility for galectin-induced malignant transformation might be via their association with the spliceosome. Indeed, galectin-1 and -3 are found in Gemin4 (C50)/SMN/Gemin2 complex and play an important role in spliceosome assembly (57). This association suggests that those galectins might regulate the processing of pre-mRNA during malignant transformation.

Apoptosis. Apoptosis regulation by galectins is probably one of their most studied intracellular functions. Several studies have shown that galectins either positively or negatively regulate apoptosis in various cancer cell models. Galectin-1 for example, increases apoptosis of LnCap prostate cancer cells, CoLo201 colon cancer cells, Leydig tumor cells and B-cell lymphomas (12,58-61). Conversely, it reduces apoptosis in gliomas, cervical and lung cancer (62-64). Galectin-3 has also been shown to modulate apoptosis. In myeloid leukemia, neuroblastoma, colorectal, breast, prostate, thyroid, bladder, pancreatic, gastric and some B-cell lymphoma cancer cells it has been shown to have anti-apoptotic functions (47,65-80). In contrast, it seems to induce apoptosis in other B-cell lymphomas (81). Galectin-7 displays a dual functionality in apoptosis as well since it reduces chemosensitivity in melanomas, breast and lymphoid cancer cells, yet it sensitizes colon, urothelial and cervical cancer cells to cell death (82-87). This role of galectin-7 in melanoma cells is clearly distinct from that of galecin-9 which rather promotes death of melanoma cells (35,88).

The underlying mechanisms of galectin's regulation of apoptosis are not fully understood. Nonetheless, many binding partners implicated in cell fate have been identified. Galectin-3 and -7 have been shown to interact *in vitro* and *in vivo* with the anti-apoptotic B-cell lymphoma-2 (Bcl-2) protein (33,89,90). The domain of galectin-7 protein implicated in this binding has not yet been identified. Still, the NWGR motif present at the N-terminus of galectin-3 protein shows a strong homology with the BH1 motif of Bcl-2, which appears to be essential for its anti-apoptotic functions (90). Due to a strong homology between the different pro- and anti-apoptotic members of the Bcl-2 family, galectins might also be able to interact with other members of the family. The modulation of either their stability or their localization would explain the dual role of galectins in apoptosis. The members of the Bcl-2 family are probably not the only galectin-binding partners implicated in apoptosis regulation. Synexin, a calcium and phospholipid-binding protein has been shown to drive the perinuclear translocation of galectin-3, which is essential to its anti-apoptotic function (91). Galectin-3 also interacts with the intracellular domain of the CD95 receptor, also known as FAS receptor

Table III. Intracellular functions of galectins in different cancers.

Galectin	Cancer type	Effect	(Refs.)
Galectin-1	Thyroid	Expression associated with malignant transformation	(50,157)
	Prostate	Increases adhesion, reduces growth rate and induces apoptosis of LnCaP cells, provoque tumor immune evasion and increases tumor vascularization. Stimulate heterotypic cell-cell adhesion	(58,108,141,158,159)
	Breast	Induces angiogenesis, tumor immune evasion and progression	(138,140,160,161)
	Colorectal	Associated with malignant progression, reduces cell migration and induces cell adhesion to ECM and apoptosis of Colo201 cells	(59,110,162)
	Cervical	Induces radioresistance, proliferation and invasion	(62,115)
	Lung	Promote chemoresistance, migration and invasion	(63,109)
	Ovarian	Increases proliferation and invasion	(64)
	Gliomas	Increases cell growth, invasion, angiogenesis and chemotherapy resistance	(51,112,113,137,163-165)
	B-cell lymphoma	Decreases viability and cell growth	(60,61)
	Melanoma	Induces cell aggregation	(166)
	Neuroblastoma	Reduces cell growth, induces immunoevasion	(93,142)
	Leydig tumor cells	Regulates positively or negatively cell proliferation and apoptosis	(12)
	Hepatic	Increases migration and invasion	(111)
	Pancreas	Promotes proliferation, invasion and immune evasion	(114,142)
Galectin-2	Breast	Increases adhesion	(116)
	Colon	Increases adhesion	(116)
Galectin-3	Colorectal	Increases metastasis formation, reduces apoptosis and induces tumor immune evasion	(65,66,125,143,167)
	Breast	Induces cell cycle arrest in response to anoikis, increases adhesion, tumor growth and protects from apoptosis	(67,68,98,168-170)
	Prostate	Induces chemoresistance, cell proliferation, angiogenesis, migration and invasion	(47,69,120,126,171)
	Thyroid	Promotes anchorage-independent growth and motility, regulate cell cycle and cell transformation, promotes chemoresistance	(70-72,172-174)
	Liver	Promotes metastasis formation	(124)
	Lung	Increases adhesion, motility, invasion and tumor immune evasion	(117)
	B-cell lymphoma	Increases resistance to fas-induced apoptosis, chemoresistance or induces apoptosis	(73,81,175,176)
	Myeloid leukemia	Reduces chemosensitivity	(74,75)
	Gliomas	Decreases cell motility and adhesion	(121)
	Melanoma	Increases metastasis formation, tumor immune evasion and angiogenesis	(122,123,139,177,178)
	Bladder	Protects cells against TRAIL-induces apoptosis	(76)
	Ovarian	Reduces cell proliferation and increases apoptosis resistance	(179,180)
	Pancreas	Increases invasion and proliferation, reduces chemosensitivity	(94,95,181,182)
	Gastric	Increses cell motility and chemoresistance	(78,118,119)
	Tongue	Increases cell proliferation, migration and invasion	(96,97)
	Neuroblastoma	Reduces apoptosis	(79)
	Renal	Reduces chemosensitivity	(80)
Galectin-4	Colorectal	Promotes adhesion, reduces cell migration and motility, induces cell cycle arrest	(100,101,183)
	Pancreas	Reduces migration and metastasis formation	(29)

Table III. Continued.

Galectin	Cancer type	Effect	(Refs.)
Galectin-7	Breast	Increases invasion, reduces chemosensitivity	(82)
	Lymphoma	Increases metastasis formation	(127-129)
	Ovarian	Increases cell proliferation	(31)
	Neuroblastoma	Reduces cell growth	(104)
	Colon	Increases chemosensitivity and reduces cell growth, anchorage-independent cell growth and angiogenesis	(83)
	Urothelial	Increases chemosensitivity	(85)
	Cervical	Increases invasive behavior *in vitro*, reduces invasion and chemoresistance	(86,87,130)
	Melanoma	Increases chemoresistance	(84)
	Gastric	Reduces cell proliferation, migration and invasion	(103)
Galectin-8	Glioblastoma	Stimulates cell migration	(131)
	Colon	Reduces tumor growth and cell migration	(106)
Galectin-9	Melanoma	Induces cell aggregation and apoptosis	(35,88,136)
	Breast	Increases cell aggregation and reduces adhesion	(36)
	Oral	Increases adhesion	(132,133)
	Colon	Increases adhesion *in vitro* but reduces metastasis formation *in vivo*	(134-136)
	Myeloma	Reduces cell growth and induces apoptosis	(105,184)
Galectin-12	Cervical	Reduces cell growth	(107)
	T-cell leukemia	Reduces cell growth	(107)

(FasR) or apoptosis antigen 1 (APO-1 or APT), leading to opposing apoptogenic mitochondrial activity (92).

Proliferation. Given their role in apoptosis, it is not surprising that galectins play a central role in the control of cell proliferation in tumors. This has been well documented in the case of galectin-1, which reduces proliferation of B-cell lymphomas, neuroblastoma and LnCap prostate cancer cells while it increases cell division of glioma, cervical, ovarian and pancreatic cancer cells (12,51,58,61,62,64,93). A similar case exists for galectin-3, which displays, once more dual functionalities in cell proliferation. For instance, galectin-3 increases proliferation of breast, prostate, pancreatic and tongue tumors (47,94-98). This might be due to the interaction of galectin-3 with the APC/Axin/β-catenin complex in the nucleus. This interaction increases the transcriptional activity of Tcf-4 transcription factor and subsequently elevates c-myc and cyclin D1 expression (99). In contrast, cytoplasmic galectin-3, along with galectin-1, bind to protocadherin-24, allowing cytoplasmic localization of β-catenin, while decreasing Wnt signaling (10). Ectopic expression of galectin-4 has also been shown to induce cell cycle arrest and to reduce cell migration/motility while sensitizing cells to camptothecin-induced apoptosis in colorectal cancer (100,101). The data from Satelli *et al* (101) suggest that galectin-4 induces downregulation of β-catenin, Dvl2, TCF1, TCF4, c-Myc, LRP6 and cyclin D1 expression levels while upregulating p21, p15 Naked 1 and Ephrin B1 (101,102). An interaction between galectin-4 and APC/Axin/β-catenin is also observed that possibly restricts the translocation of the complex to the nucleus. This results in a downregulation of Wnt signaling and a decrease in proliferative potential of colon cancer cells. In contrast, galectin-7 seems to exhibit an increased proliferative activity in ovarian cancer cells, whereas it reduces the proliferation rate of neuroblastomas, colon and gastric cancer cells (31,103,104). Galectin-8 and -9 have been shown to reduce colon and myelomas tumor growth, respectively (105,106). Galectin-12, for its part, reduces the proliferation of T-leukemia and cervical cancer cells (107). Such contradictory roles for galectins in cell proliferation suggest that extreme precaution must be taken in order to target intracellular galectins in cancer.

Adhesion, migration and invasion. The metastatic behavior of cancer cells is initiated by dysregulation in cell adhesion, migration and invasion abilities. Alterations of interactions between extracellular transmembrane receptors and galectins are often seen in malignancies and late stages of carcinomas. For instance, galectin-1 increases adhesion of colorectal and prostate cancer cells (59,108) and stimulates migration of hepatic and lung cancer cells, while reducing colorectal cell migration (63,109-111). It also increases the invasive behavior of gliomas, lung, ovarian, hepatic, pancreatic and cervical cancer cells (51,63,64,109,111-115). The ability of galectins to increase adhesion and migration has been well documented in the case of galectin-2 and most notably in the case of galectin-3 (47,67,97,116-120). Specifically, galectin-3 reduces glioma cell migration (121). In general, however, galectin-3

Table IV. Intracellular ligands of galectins.

Galectin	Binding partners	CRD/non-CRD binding	Effect	(Refs.)
Galectin-1	H-Ras		Increased membrane anchorage of Ras and GTP bound state resulting in cell transformation	(52)
	Gemin4 (C50)/SMN/ Gemin2 complex		Supply functional snRNPs to the H/E complex in the pathway of spliceosome assembly	(57)
	Protocadherin-24		Localization of β-catenin to the cell membrane resulting in decreased Wnt signaling	(10)
	Monomeric actin	CRD	Polymerization-depolymerization of actin in platelet aggregation	(185,186)
Galectin-3	ATP synthase		Inhibition of ATP synthase activity and cell cycle progression to G0/G1 phase	(25)
	Protocadherin-24		Localization β-catenin to the cell membrane resulting in decreased Wnt signaling	(10)
	CD95 (APO-1/Fas)	Non-CRD	Induction of apoptogenic activity at the mitochondria	(92)
	Nucling		Increase sensitivity to apoptosis	(187)
	Synexin		Decrease sensitivity to apoptosis	(91)
	CBP70	CRD	ND	(188)
	β-catenin/TCF complex	NH2 and COOH termini	Induction of transcriptional activity of Tcf-4 with an increase in c-Myc + cyclin D1 expression	(99)
	Axin/β-catenin/APC	Consensus sequence (S92XXXS96)	Promotion GSK-3β-dependent phosphorylation of galectin-3/β-catenin resulting in a decrease in Wnt signaling	(147)
	TTF-1		Upregulation of transcriptional activity of TTF-1 contributing to cellular proliferation	(189)
	K-Ras		Increase Raf-1/PI3K signaling and attenuated ERK signaling	(53,54)
	Bcl-2	Non-CRD (NWGR motif)	Apoptosis-suppressing activity and increase mitochondrial integrity and decrease caspase activation	(89,90)
	Alix/AIP-1		Facilitation of pro-apoptotic signaling (Ca^{2+} dependent)	(190-192)
	Gemin4 (C50)/SMN/ Gemin2 complex		Supply functional snRNPs to the H/E complex in the pathway of spliceosome assembly	(57)
	Chrp	CRD	ND	(193,194)
Galectin-4	β-catenin/APC/Axin		Increase Naked 1 which destabilizes Dsh/Dvl proteins resulting in a decreased Wnt signaling	(101,102)
Galectin-7	Bcl-2		Sensitize mitochondria to apoptosis signals	(33)
	Smad 3		Decrease expression of TGF-β responsive genes resulting in an anti-fibrotic effect on liver tissue	(195)

is mostly associated with increased invasive behavior in most cancer cell types tested (94,95,117,122-126), supporting the view that targeting this galectin might be a promising avenue for the treatment of many types of cancer. Whether this is also true for other galectins has to be determined. On the contrary, galectin-4 was found to promote adhesion of colorectal cells and to reduce migration and metastasis formation of colorectal and pancreatic cancer cells (29). Further, conflicting functionalities are once again displayed in the case of galectin-7 dependent on the cell type. Particularly, galectin-7 reduces migration of gastric cancer cells and invasion of urothelial and gastric cancer cells (85,103) while it is associated with increased invasion of other types of cancer, including breast cancer and T-cell lymphoma (82,127-130). Galectin-8 also seems to have different abilities to modulate migration, most notably in glioblastoma and colon cancer cells (106,131). A similar scenario exists for galectin-9, which increases adhesion of melanoma, oral and colon cancer cells, but reduces adhesion of melanoma and breast cancer cells and metastasis formation of colon cancer cells (35,36,132-136). How galectin positively or negatively modulates the invasive behavior of cancer cells remains largely unknown. There are some indications that galectins may increase the secretion of extracellular proteases, remarkably in the case of galectin-7, which induces the upregulation of matrix metalloproteinase-9 (MMP-9) gene expression, possibly through the p38 mitogenic-activated protein kinase (MAPK) (128,130). Unlike apoptosis, however, the identification of the intracellular binding partners that are involved in the modulation of the invasive behavior of cancer cells remains unknown. In contrast, extracellular galectins and their respective binding partners have been fairly well characterized.

Other functions of galectins. Angiogenesis is also among the functions associated with galectin activity. For example, galectin-1 increases glioma, prostate and breast tumor vascularisation (108,137,138). Galectin-3 also increases vascularisation of prostate tumors and melanomas, while galectin-7 reduces angiogenesis of colon tumors (47,83,139). Galectins have been shown to take part in the tumor immune escape. Indeed, galectin-1 promotes immunoevasion of neuroblastoma, prostate, breast and pancreatic cancer cells (140-142). Galectin-3 also increases tumor immune escape of melanomas, colorectal and lung cancer cells (117,123,143). Most studies suggest that extracellular galectins are responsible for these functions. The involvement of intracellular galectins in these processes remains unknown.

4. CRD-independent functions for intracellular galectins?

Galectins are primarily known for their ability to bind to glycans containing lactose or N-aceyllactosamine via Van der Walls interactions between the carbohydrate and binding pocket. They have a relatively broad specificity depending on the type and the length of the carbohydrate and the mode of presentation of ligand to the CRD. It is thus logical to assume that inside the cells, they will also preferentially bind to intracellular glycoconjugates, which are abundantly found in the cytosol. There is compelling evidence, however, that galectins might have non-carbohydrate binding partners and functions. CRD-independent functions have been particularly well documented for intracellular galectins (144-146). For example, galectins do interact with Bcl-2 family members via a CRD-independent interaction (33,85,89,90). This galectin/Bcl-2 interaction is important since the balance of activity between pro- and anti-apoptotic signals of members of the Bcl-2 family regulates apoptosis. Other CRD-independent functions of galectins include RNA processing in the nucleus (57) and regulation of cell cycle progression (Wnt signaling?) (25,99,101,102,147). All these galectin functions are independent of their saccharidic binding activities and rather rely on protein-protein interactions. Some galectins, such as galectin-10, harbor very low affinity for galactosides and are believed to act mainly through other specificities, while their CRD binding activity remains debated (148,149). These CRD-independent functions represent a paradigm shift in our understanding of galectin function and the development of galectin-specific antagonists.

A new challenge: studying the redundancy of galectin functions. The existence of redundant or antagonistic functions between galectins is a major concern because these proteins can converge under normal or pathological conditions. The cross-talk between intracellular galectins remains completely unknown although cells often express more than one intracellular galectin. For example, MCF-7 breast cancer cells express galectin-3, -8 and -9 (150). MCF-10 and MDA-MB-468, two other human mammary epithelial cell lines, express both galectin-3 and -7, but not galectin-8 or -9 (151,152). Moreover, many galectins could be present within the same intracellular compartments. A case in point is the mitochondria, where both galectin-3 and -7 are found. Galectin-12 can also be present in mitochondria and not surprisingly, it seems to be involved in the control of cellular metabolism (38-40). Whether galectins have redundant or opposed functions in the mitochondria is an interesting question given the critical role of cellular metabolism in cancer. A better understanding of the functional redundancy among homologous proteins, which is frequently observed in eukaryotes, is also critical. Such redundancy often occurs in order to increase maintenance of important gene function and to limit losses following mutations/deletions of specific genes (functional compensation). Lessons learned from such studies could also bring important insight into many others fields, from understanding pathologies to general developmental biology.

Future directions. Because of their critical role in cancer, considerable efforts have been directed towards the development of carbohydrate-based inhibitors that would limit the binding of galectins to glycosylated residues on cell surface receptors. For example, GCS-100 is a galectin-3 antagonist with a modified citrus pectin carbohydrate that has been shown to inhibit tumor growth and metastasis in several preclinical models (153-155). Others, like OTX008, a galectin-1 antagonist, act as allosteric CRD-dependent inhibitors following binding to a site distant from the carbohydrate-binding site (156). Nevertheless, despite almost two decades of research, the development of effective galectin antagonists for the treatment of cancer has met with limited success. The emerging evidence that galectins have critical intracellular and CRD-independent functions calls for a refocusing of our efforts on development of new galectin-specific antagonists to modulate apoptosis. Our knowledge of the subcellular localization of galectins will also significantly improve target identification during the drug discovery process. It is thus imperative to better understand the role of intracellular galectins and to provide novel insight into how galectins collaboratively modulate cancer progression from within the cells.

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