[Frontiers in Bioscience 17, 438-450, January 1, 2012]

A distinctive role for galectin-7 in cancer ?

Yves St-Pierre[1], Carole G. Campion and Andree-Anne Grosset[1]

[1]INRS-Institut Armand-Frappier, Universite du Quebec, 531 Blvd des Prairies, Laval, Quebec, Canada, H7V 1B7

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Galectin-7: Comparison with other members of the galectin family
3.1. Galectins
3.2. Distinctive expression pattern of galectin-7
3.3. Cellular localization of galectin-7
4. Galectin-7 in cancer
4.1. The pro-apoptotic function of galectin-7: a logical role in suppressing tumor growth
4.2. Unexpected roles of galectin-7
4.3. Galectin-7: a marker for mammary myoepithelial cells and aggressive breast cancer?
5. Other functions for galectin-7
6. Concluding remarks
7. Acknowledgement
8. References

1. ABSTRACT

The galectins are a family of evolutionay-conserved carbohydrate-binding proteins. They are distributed widely in all living organisms and have been implicated in many essential functions including development, differentiation, cell–cell adhesion, cell–matrix interaction, growth regulation, apoptosis. Several members of the galectin family have also been shown to be involved in cancer progression and metastasis. In the case of galectin-7, several studies have reported alterations in its expression pattern during cancer progression. In a variety of tumors, its expression can range from being completely down-regulated to highly up-regulated. Accordingly, its precise role in this field is still debated. The evidence shows that galectin-7 may promote or inhibit cancer development. In this article, we review the data concerning expression and roles of galectin-7 in cancer and propose a comprehensive view of its contribution during cancer progression.

2. INTRODUCTION

In recent years, cancer-associated changes in protein glycosylation have generated considerable interest. Accordingly, carbohydrate-binding proteins (lectins) that are present in the extracellular matrix (ECM) and have high affinities for specific oligosaccharide structures expressed on the cell surface have emerged as promising markers for and therapeutic targets in a large number of diseases, including cancer. This is particularly true for members of the galectin family. A role of galectins in cancer invasion and metastasis has been well documented. However, most of the attention has been focused on galectin-1 and galectin-3, and thus we still know very little about how galectin-7 expression affects cancer progression and how distinctive its role is. Although most studies report that galectin-7 is associated with apoptosis, a number of observations suggest that it may paradoxically promote disease progression. Here, we offer an explanation for this paradox and discuss data suggesting that galectin-7 may

Table 1. Cell-specific expression of galectin-7 in normal tissues

Tissue	Cell type	Localization	References
Oral mucosa	Squamous epithelial cells	Nuclear and cytoplasmic/membranous	(80)
Skin	Epidermal cells and outer root sheath of the hair follicle	Nuclear and cytoplasmic/membranous	(10, 13, 14, 80, 81)
Cervix	Squamous epithelial cells	Nuclear and cytoplasmic/membranous	(80, 82)
Vagina	Squamous epithelial cells	Nuclear	(80, 82)
Vulva/anal skin	Squamous epithelial cells	Nuclear and cytoplasmic/membranous	(80)
Ovary	Stroma epithelial cells and epithelial cells of the surface	Nuclear and cytoplasmic/membranous	(14, 83)
Breast	Myoepithelial cells	Nuclear and cytoplasmic/membranous	(15, 63)
Forestomach	Squamous epithelial cells	Nuclear and cytoplasmic/membranous	(13, 17)
Hypopharynx and larynx	Epithelial cells	Nuclear and cytoplasmic/membranous	(45)
Bladder and Urogenital ridges	Urothelial cells, predominantly those near the external urethral orifice	Cytoplasmic	(16, 84, 85)
Esophagus	Epithelial cells	Nuclear	(13, 86) (82)
Colon (upper crypts)	Epithelial cells	Nuclear	(83)
Trachea	Epithelial cells	Nuclear and cytoplasmic/membranous	(14)
Tongue	Squamous epithelial cells	Nuclear and cytoplasmic/membranous	(13, 87)
Lip	Sebaceous glands	Cytoplasmic/membranous	(13, 87)
Artery	Intima	Nuclear and cytoplasmic/membranous	(88)
Cornea	Epithelial cells	Nuclear and cytoplasmic/membranous	(13, 49)
Thymus	Epithelial cells of Hassal's corpuscules	Nuclear and cytoplasmic/membranous	(13)

serve as a novel marker for and a therapeutic target in some forms of cancer.

3. GALECTIN-7: COMPARISON WITH OTHER MEMBERS OF THE GALECTIN FAMILY.

3.1. Galectins

Galectins constitute a family of lectins defined by shared consensus amino acid sequences and affinities for beta-galactose-containing oligosaccharides (1). In humans, galectins are numbered according to the order of their discovery, and the 15 members of the family are normally classified according to their structure and number of carbohydrate recognition domains (CRD) (2,3) . The galectins have either one (Galectin-1, -2, -5, -7, -10, -11, -13, -14, and -15) or two (Galectin-4, -6, -8, -9, and -12) CRD linked by a hinge peptide. Typically, CRD are located in the C-terminal end of a protein and consists of a typical β-sandwich fold of approximately 130 amino acid residues that are conserved in all galectins and that include a glycine which stabilizes galectin–carbohydrate interactions (4-7). Analysis of the three-dimensional structure of galectin-7 reveals its homology to galectin-1 and galectin-3, although its overall structure more closely resembles galectin-10, a lysophospholipase expressed primarily in eosinophils, basophils, and some T cells (8, 9). Although early reports suggested that galectin-7 was a monomer (10), further analyses of its crystal structure and its aggregation properties by mass spectrometry indicated that it has the ability to form homodimers (11, 12).

3.2. Distinctive expression pattern of galectin-7

Unlike other most commonly studied galectins, galectin-7 exhibits a high degree of tissue specificity; its expression is restricted mostly to stratified epithelial cells of the esophagus, tongue, lip, and epidermis (13, 14). Galectin-7 is found in several types of epithelial cells, including epithelial cells of hair follicles, the esophagus, the oral epithelia, the cornea, Hassall's corpuscles of the thymus, the urinary system, the stratified squamous epithelium of the forestomach, and mammary myoepithelial cells (13, 15-17) (Table 1). Accordingly, high levels of galectin-7 are found in HaCaT cells, a transformed keratinocyte cell line, and in MDA-MB-468, a human breast cancer cell line. Although aggressive lymphoma cells may express galectin-7 constitutively, cell lines derived from the lymphoid and myeloid lineages, such as Jurkat T lymphoma cells, do not express detectable levels of galectin-7 (18, 19).

Although a number of stimuli have been shown to positively or negatively regulate galectin-7 expression in different cell types (Tables 2 and 3), the molecular mechanisms regulating the cellular specificity of galectin-7 expression remain poorly characterized. The expression of galectin-7, like that of other members of the galectin family, is partially controlled by epigenetic mechanisms, such as DNA methylation (20-23). This conclusion is largely based on experiments showing that treatment of cell lines with DNA methyltransferase inhibitors, such as 5-aza-2'-deoxycytidine (5-aza-dC), can induce galectin-7 expression in cells that do not normally express the protein, such as Jurkat T lymphoma cells and HCT116 colon cancer cells (18, 24). Genome profiling experiments comparing several cell lines and primary cells (such as primary dermal fibroblasts) with or without 5-aza-dC treatment have also revealed a possible link between DNA hypomethylation and galectin-7 expression (25-27). A positive correlation between the hypomethylation state of the galectin-7 promoter and constitutive expression of galectin-7 has also been reported (24). Whether DNA hypomethylation favors the binding of specific transcription factors to the galectin-7 promoter is currently unclear. In fact, the identity of the transcription factors that regulate galectin-7 expression remains largely unknown. Results from gene profiling experiments indicate, however, that a number of transcription factors may be involved in inducing or repressing galectin-7 expression. The first transcription factor shown to regulate galectin-7, at least in colorectal cancer cells, was p53 (28). A study from the group of Bert Vogelstein revealed that *galectin-7* mRNA was one of the 14 transcripts (or "PIG's", for *p53-induced genes*) out of

Table 2. Stimuli that increase galectin-7 expression

Compound	Specificity	Model system	References
Dimethyloxalylglycine	2-oxoglutarate (2-OG) dependent dioxygenase inhibitor	Human mammary MCF-7 tumor cells	(89)
5'-deoxyazacytidine	DNA methyltransferase inhibitor	Lymphoma cells	(24)
p63	Transcription factor	p63 null mutation and its effect on skin	(90)
Early growth response factor 1 (EGR1)	Transcription factor/hormone	Human umbilical vascular endothelial cells (HUVECs)	(91)
Keratinocyte growth factor (KGF) and Epidermal growth factor (EGF)	Hormone	Skin of C57/Bl6J mice treated with EGF and KGF	(92)
Ultraviolet (UV) B rays	-	Human epidermal keratinocyte	(48)
p53	Transcription factor	Overexpression of p53 in human DLD-1 and CRC colorectal cancer cells	(28)
H/Ras	Signaling pathway	H/Ras-induced genes dependent on p65 and/or c-Rel in immortalized mouse embryo fibroblasts (MEFs)	(93)

Table 3. Agents that suppress galectin-7 expression

Compound	Specificity	Model system	References
Estrogen	Hormone	Human mammary MCF-7 tumor cells	(94)
GATA-3	Transcription factor	Human mammary MCF-10A tumor cells	(95)
Glucocorticoid receptor	Hormone	Human mammary MCF-10A tumor cells	(96)
Epigallocatechin gallate (EGCG)	NA	NF639 breast cancer cell	(97)
Luteinic hormone	Hormone	Bitransgenic mice overexpressing ERB2/Neu and LH	(98)
Parthenolide	NF-□B Inhibitor	Human keratinocytes	
miRNA-34	miRNA	Human HCT116 colorectal cancer cells	(99)
Retinoic acid	Hormone	Human epidermal keratinocytes	(100)

7,202 induced in DLD-1 colorectal cancer cells following *de novo* expression of p53. *In silico* analysis of its promoter does indeed reveal the presence of p53 consensus sites proximal to the initiation sites. *Galectin-7* may also be a target gene of p63 during early epidermal morphogenesis (29). The p63 isoforms are homologs of p53 and are capable of activating gene expression by binding to degenerate p53 response elements. The ability of p53 alone to induce galectin-7 may, however, be cell type-dependent, because induction of p53 by doxorubicin in lymphoma cells is insufficient to induce galectin-7 expression (18). Computational analysis of the human and mouse *galectin-7* promoters reveals the presence of several conserved consensus sites, including those for NF-κB subunits and GATA-3. These transcription factors are among the prime candidates for regulation of *galectin-7* expression. We have identified an inverse relationship between GATA-3 and galectin-7 expressions in mammary tumor cells (15). A relationship between NF-κB, which is a major anti-apoptotic factor (31), and galectin-7 was also reported recently, in a series of gene pathway profiling experiments aimed at identifying networks of molecular interactions of genes expressed in highly metastatic variants of 4T1-derived breast tumors (32). Whether these transcription factors play a role in galectin-7 expression in specific cell types and/or cancer remains, however, to be established.

3.3. Cellular localization of galectin-7

Historically, the cellular localization of galectins has been a subject of intense scrutiny, given the multiple roles of these proteins. A general assumption is that galectins exist in extracellular and intracellular compartments. Although they do not harbor a signal sequence, the members of galectin family can be secreted through a non-classical secretory pathway, sometimes in galectin-rich vesicles or cell-derived exosomes following exocytic fusion with plasma membranes (33-35). Consequently, they have often been found in the sera of normal subjects and cancer patients. For example, normal individuals have detectable levels of galectin-3 in their serum, while patients with metastatic disease have significantly higher levels of galectin-3 compared to normal individuals or patients with localized tumors (36-38). ELISAs have also been used to demonstrate secretion of galectin-1 into the culture medium by a number of different cell types, including specific subsets of B and T cells, endothelial cells, and multipotent mesenchymal stromal cells (39-42). Accordingly, recombinant galectins have been extensively used to study various carbohydrate-dependent extracellular functions in various *in vitro* model systems. These studies have shown that secreted forms of galectins bind and crosslink widely expressed cell surface receptors harboring the appropriate oligosaccharides. Such oligomeric interactions create lattices or microdomains that regulate glycoprotein mobility in the plane of the membrane (43). For example, the binding of galectin-3, -8, or -9 to β1,6GlcNAc-branched N-glycans on the extracellular surface of the EGFR induces the formation of a transient dynamic lattice that opposes receptor loss through endocytosis, thus maintaining its sensitivity to ligand binding (44). To our knowledge, however, there is no indication that galectin-7 participates in the formation of such structures. This may be due to the fact that galectin-7 is preferentially found in intracellular compartments. Although cell binding studies using recombinant galectin-7 has revealed that galectin-7 binds to the cell surface in a carbohydrate-dependent manner (12) and can stimulate MMP-9 expression (19), most studies have reported that galectin-7 expression is restricted to the cytoplasm and the nucleus (Table 1). Our group and others have also failed to detect significant levels of galectin-7 in sera from both healthy individuals and cancer patients (45). Analyses of supernatants from HaCaT or mammary epithelial cells lines using either ELISAs or western blots have also failed to provide evidence for a secreted form of galectin-7 in these cells, even when galectin-7 is expressed at high levels into the cytoplasm following transfection with an expression vector encoding human or mouse galectin-7 (15). Similarly,

no immunoreactivity could be detected in COS-1 or HeLa cells transfected with a cDNA encoding galectin-7 (10, 46). Galectin-7 seems to be preferentially found in intracellular compartments, possibly interacting with the cytoskeleton (10). Although the reason why galectin-7 (in contrast to other galectins) cannot be detected in the serum is currently unclear, we believe that investigation of the role of galectin-7 in normal and pathological processes should focus on intracellular compartments rather than extracellular spaces.

4. GALECTIN-7 IN CANCER

4.1. The pro-apoptotic function of galectin-7: a logical role in suppressing tumor growth

Members of the galectin family are well known for their ability to promote apoptosis, and a large number of reviews have documented the role of galectins in apoptosis. Based on the idea that galectin-7 shares functions with its family, most of the investigations concerning galectin-7 have thus focused on its implication in apoptosis. This link between apoptosis and galectin-7 was initially proposed in the study linking induction of its expression to that of p53 in colon cancer cells (28). Given its preferential distribution in epithelial cells, the ability of galectin-7 to modulate apoptosis was believed to play an important role in epidermal homeostasis, since apoptosis is an essential mechanism for maintaining epidermal integrity (13, 47). This role was further supported by a study by Bernerd et al., (48) who reported that both mRNA and protein levels of galectin-7 were increased in cultured keratinocytes after UVB radiation. They also found that sunburned/apoptotic keratinocytes expressed higher levels of galectin-7 than other keratinocytes and that galectin-7 overexpression induces a significant increase in terminal deoxynucleotidyltransferase-mediated UTP end labeling (TUNEL)-positive keratinocytes. It is thus not surprising that galectin-7 plays a role in epithelial cell migration and in the re-epithelization of corneal and/or epidermal wounds (49-51). Such a role for galectin-7 in the homeostatic control of epithelia is supported by recent studies using galectin-7-deficient mice. Using these mice, Gendronneau et al. (52) showed that galectin-7 helps to maintain epidermal homeostasis in response to UVB irradiation and wounding. Ectopic expression of galectin-7 in DLD-1 cells also made them more sensitive to a number of different apoptotic stimuli (53). Moreover, DLD-1 transfectants overexpressing galectin-7 grew significantly slower than control transfectants, most notably following injection into severe combined immunodeficient (SCID) mice. This anti-proliferative effect of galectin-7 does not seem to be restricted to colorectal cancer cells, because galectin-7 also renders HeLa cells more sensitive to apoptotic stimuli (46). These studies also showed that galectin-7's pro-apoptotic function was most likely performed by its intracellular form, because it was found to localize in the nuclei and cytoplasm in various cell types, including HeLa and HaCaT cells. Galectin-7 is thus distinct from other members of the galectin family with regards to the mechanisms by which they modulate apoptosis. Galectin-1 and galectin-9, for example, induce tumor cell apoptosis when added to the extracellular space, whereas galectin-7, galectin-3, and galectin-12 seem to promote apoptosis through intracellular mechanisms (54).

This ability of galectin-7 to inhibit cell proliferation may not always be linked to its pro-apoptotic function. Galectin-7-mediated inhibition of proliferation in neuroblastoma cells, for instance, can be achieved without any signs of apoptosis (12). In this case, the anti-proliferative effect seem to be mediated through extracellular binding of recombinant galectin-7 to specific cell surface receptors and could be blocked by addition of extracellular galectin-3, supporting the idea that galectin-7 and galectin-3 may have distinct functions. The specific identity of these surface receptors involved remains unclear, however. Because recombinant galectin-7 can bind non-reducing terminal LacNac residues on cell surface receptors as well as internal LacNac oligosaccharide residues (55), the number of receptors that could potentially bind extracellular galectin-7 is relatively large.

4.2. Unexpected roles of galectin-7 in cancer

At first glance, it seems that, given its link with apoptosis and its anti-proliferative effects, galectin-7 should have a negative role in tumor progression. Observations made in several experimental model systems suggest, however, that galectin-7 expression is increased in tumors and may thus favor tumor progression (Table 4). The first hint that galectin-7 may be associated with tumor progression was found in a study reported by Lu et al. (56). Using an experimental rat model of chemically induced mammary carcinoma, Lu and colleagues found that galectin-7 was overexpressed in mammary tumors as compared to normal mammary tissues. Our work in lymphoma and breast cancer also support the possibility that galectin-7 may promote tumorigenesis. In lymphoma, we have shown that galectin-7 expression was induced in aggressive T lymphoma cells generated upon in vivo passages on non-aggressive lymphoma cells in syngenic immunocompetent mice (18). Such a strategy for generating highly metastatic tumor cell lines has been successfully used in the past to identify genes that are involved in tumor progression (for examples, see (57) and (58)). Similar increases in the level of galectin-7 were found in a significant proportion of mature human B-cell lymphoid neoplasms but not in normal B lymphocytes (59). This abnormal expression of galectin-7 is believed to favor dissemination of lymphoma cells; mice injected with T lymphoma transfectants expressing high levels of galectin-7 developed large metastatic tumors in the liver and kidneys with massive infiltration of tumor cells in the parenchyma as compared to mice injected with control lymphoma cells (19). In contrast, only a few scattered tumor foci with limited infiltration were observed when galectin-7 expression was suppressed in highly aggressive lymphoma cells (59). The ability of galectin-7 to induce expression of *MMP-9*, a gene known to confer clinical aggressiveness upon lymphoma cells, may in part explain this capacity of galectin-7 to increase metastasis. This hypothesis is supported by a number of experiments in human cancer (Table 5). Additionally, galectin-7 may confer resistance to apoptosis (15). Indeed, galectins do not always induce or promote apoptosis. For example, it is

Table 4. Galectin-7 in experimental cancer model systems

Tissue/cells	Model systems	Treatment	Observations	References
Mammary tumor tissues	Rat	NMU-induced mammary tumors	Increased expression of galectin-7 in mammary tumors	(56, 101)
Lymphoma	Mouse	5-AZA-deoxycytidine	Increased expression of galectin-7	(24)
Immune-resistant cancer cells	Mouse	Tumor vaccine	Increased galectin-7 expression in immune-resistant cancer cells	(102)
Lymphoma	Mouse	*In vivo* selection	Increased galectin-7 expression in aggressive variant	(18)
Fibrosis	Hepatic stellate cells (HSC) and transgenic mice harboring alpha2(I) collagen gene (COL1A2) promoter	Hepatocyte growth factor	HGF accelerated nuclear export of Smad3 by enhancing its interaction with galectin-7	(76)
Urothelial cancer	Bladder cancer cell lines with various p53 statuses	Chemotherapeutic cis-diamminedichloroplatinum (CDDP)-	Exposure to CDDP induced galectin-7 expression in cell lines with wild-type p53 but not in those with mutated p53	(103)
Acute myeloid leukemia	Cytarabine (Ara-C)-resistant cell lines	Cytarabine (Ara-C), a chemotherapeutic agent for acute myeloid leukemia	Increased expression of galectin-7 in cell lines that were resistant to Ara-C	GDS1907Il
Retinoblastoma	Retinoblastoma cell lines	Cisplatin	Decreased expression of galectin-7 in the presence of cisplatin	(104)
Breast cancer	Breast cancer lines ME16C and HME-CC	Doxorubicin or 5-fluorouracil	Increased expression of galectin-7 following treatment	(105, 106)
Kidney	Male Syrian hamster kidney (SHKT) (animal model for the study of estrogen-dependent renal malignancies)	Diethylstilbestrol (DES)	Increased expression of galectin-7 in large renal tumors induced by DES	(107)
Skin tumors	Transgenic mouse	Overexpression of Insulin-like growth factor-1 (IGF-1) in transgenic mice	Overexpression of galectin-7	(108)
Colorectal cancer	Human colon carcinoma cells DLD-1	Overexpression of galectin-7	Suppression of tumor growth and angiogenesis	(53)

Table 5. Modulation of galectin-7 expression in human cancers

Cancer	Normal tissue	Tumor	Role	References
Hematological malignancies	Undetected in B and T lymphocytes	High levels in several hematological disorders, including CLL and follicular lymphoma	Galectin-7 increases the metastatic behavior of lymphoma cells and induces expression of MMP-9	(18, 19, 109, 110)
Breast Cancer	Specifically expressed in myoepithelial cells	Expressed in basal-like and HER-2 positive breast cancers	Increases metastasis to bones and lungs; induces resistance to EGCG-induced apoptosis	(15, 63, 111)
Skin cancer	Expressed in all layers of the epidermis, more intensively in the basal layer	Expressed in benign nevi and melanoma in situ; undetected in basal cell carcinomas and malignant melanoma	Decreased in metastatic melanoma	(10, 112-115)
Esophageal cancer	Expressed in normal esophageal epithelial tissues	Highly expressed in esophageal squamous cell carcinomas	Associated with well-differentiated tumors	(86)
Cervical cancer	Moderately expressed in squamous epithelial cells	Expressed in cervical cancer tissue	Associated with concurrent chemoradiotherapy sensitivity; increases activation of p38 MAPK, expression of MMP-9 and invasion; decreased expression in cervical intraepithelial neoplasia compared to normal tissue	(80)(116-119)
Thyroid cancer	Undetected in glandular cells	Expressed in multinodular goiters and adenomas and at significantly higher levels in carcinomas	Distinguishes microfollicular adenomas from the encapsulated follicular variant of papillary thyroid carcinomas (high galectin-7 expression)	(80, 120, 121)
Hypopharyngeal and laryngeal cancer	Expressed in epithelial cells	Expressed in hypopharyngeal and laryngeal squamous cell carcinomas	High levels of galectin-7 associated with rapid recurrence rates and dismal prognosis; associated with tumor progression; positive correlation with differentiation and keratinization; positive correlation between MMP-9 and galectin-7 expression in laryngeal tumors	(45, 112, 122, 123)
Lung cancer	Undetected in alveolar cells	Expressed in xenografts of small cell lung cancer cells and in squamous cell carcinoma (non-small cell lung cancer)	Increases in derived cell lines and in secondary xenografts derived from those cell lines	(80, 124-126)
Colon	Undetected in glandular cells	Undetected in colorectal cancer	Galectin-7 induces sensitivity to apoptotic stimuli, negatively regulates cell growth, and retards tumor growth in vivo	(80, 127)
Buccal cancer	Moderately expressed in squamous epithelial cells	Expressed in buccal squamous cell carcinoma (SCC)	Increases in buccal SCC compared to normal tissue	(80, 128)
Neuroblastoma	No data	No data	Reduces cancer cell proliferation by acting on the cell surface	(12)
Bladder cancer	Weakly expressed in urothelial cells	Expressed in bladder squamous cell carcinomas at variable levels	Associated with well-differentiated tumors; induces sensitivity to cisplatin by accumulation of ROS and activation of JNK and BAX; correlates with muscle-infiltrating growth	(84, 129, 130)
Kaposi's Sarcoma	Expressed in epithelial cells of the skin	Expressed in epithelial cells of the AIDS-related Kaposi's sarcoma	No data	(131)

well-known that galectin-3 is associated with resistance to apoptosis in a large number of cell types and diseases, including cancer, and in response to various pro-apoptotic stimuli (reviewed in (60)). Such mechanisms may also explain the ability of galectin-7 to promote metastasis of breast cancer cells to the bone and lung. Using well-characterized breast cancer models, we have found that *de novo* expression of galectin-7 in 4T1 and 66c14 mammary epithelial cells increases their metastatic potential when injected into syngenic Balb/c mice (15). Again, as we observed in lymphoma, aggressive variants of 4T1 mammary cells that metastasize to the bone express higher levels of galectin-7 than their non-aggressive counterparts.

4.3. Galectin-7: a marker for mammary myoepithelial cells and aggressive breast cancer?

In humans, invasive breast carcinomas can be categorized into the following distinct subtypes: luminal A, luminal B, HER2-positive, and basal-like (61)(62). While luminal A and luminal B breast cancer subtypes express the estrogen receptor (ER) and/or progesterone receptor (PR), HER2-positive and basal-like subtypes are hormone receptor negative and have a more aggressive phenotype and a worse prognosis than luminal-type breast carcinomas (61-64). Immunohistochemical experiments using anti-galectin-7 specific antibodies on tissue microarrays (TMAs) constructed from samples obtained from normal breast tissues and breast carcinomas revealed that galectin-7 is exclusively expressed in HER2-positive and ER/PR-negative basal-like breast cancer (15). Not surprisingly, many human basal-like breast cancer cells, such as MDA-MB-468, express galectin-7 constitutively (Y. St-Pierre, *unpublished*). In contrast, most human or mouse breast cancer cell lines with luminal characteristics do not express galectin-7. Interestingly, we also have found that galectin-7 was specifically expressed in mammary myoepithelial (or basal) cells but not in mammary luminal epithelial cells (15). Overall, it is clear that this expression pattern is different from that other galectins, such as galectin-3, which is specifically expressed in normal luminal epithelial cells (65). Moreover, in contrast to galectin-7, galectin-3 is downregulated during breast cancer progression (66). Thus, if we consider galectin-7 a specific marker of myoepithelial cells (as opposed to luminal cells), this pattern of expression would be consistent with the hypothesis that basal-like breast cancer originates from myoepithelial cells (67). This hypothesis remains controversial, however, because several other markers that are specifically expressed in myoepithelial cells are not expressed in basal-like breast cancers (68). How the luminal and myoepithelial lineages are maintained is currently unclear, although recent work indicates that expression of GATA-3 is essential for luminal differentiation (69). Interestingly, we found that overexpression of galectin-7 is related to absence of GATA-3 (15). These observations, which concerned the protein level, are corroborated by results obtained at the mRNA level in several microarray analyses aimed at defining specific markers for myoepithelial cells or basal-like breast cancers. Microarray studies on normal breast luminal and myoepithelial cells from Jones et al. identified *galectin-7* as a myoepithelial-specific gene (70). In fact, *galectin-7* ranked first on the list among the 42 most predictive genes that distinguish luminal from myoepithelial cells. A close examination of the genomic profiling data reported by Perou et al., (63), who provided a molecular portrait of 65 surgical specimens of human breast tumors from 42 individuals, reveals that galectin-7 transcripts are highly expressed in cell lines with a basal-like phenotype. Whether the association between galectin-7 and aggressive breast cancer and the ability of galectin-7 to promote metastasis are linked to MMP-9, as is the case in lymphoma, remains to be tested. Interestingly, in breast cancer, suppression of *MMP-9* expression using RNAi technology resulted in complete regression of orthotopic breast tumors in nude mice (71). Similarly, ablation of MMP-9 expression by RNAi inhibits tumor invasion in human breast cancer cells (72). Such a possibility is reminiscent of another major role played by galectins – that of promoting cancer cell migration and leading to the formation of metastases. Levels of galectin-1, -3, and 8, for instance, have been shown to modulate cell-cell and cell-ECM contacts during migration to promote integrin-mediated cell adhesion and migration of tumor cells and leukocytes at different stages of metastasis (54, 73-75).

5. OTHER FUNCTIONS FOR GALECTIN-7

Given its specific cellular distribution, it is logical to believe that while galectin-7 shares some functional characteristics with other members of the galectin family, it may fulfill different specific functions in specific cell types (notably in epithelial cells, where it is highly expressed). For instance, galectin-7 is believed to counteract TGFβ-mediated effects (76). During their investigations aimed at elucidating how hepatocyte growth factor (HGF) antagonizes TGFβ in hepatocytes, Inagaki and colleagues (76) showed that galectin-7 physically interacts with activated forms of Smad2/3, modulating their nuclear export. In the absence of HGF, Smad2 and 3 are responsible for the induction of COL1A2 following TGFβ stimulation. Such a role for galectin-7 may not be entirely specific; at least one another member of the galectin family, galectin-1, has been shown to interfere with the TGFβ pathway, possibly by preventing Smad2/3 from binding to its specific binding site on the *COL1A2* promoter (77). Physical interaction between galectin-1 and Smad proteins in the nucleus has not, however, been confirmed. On the other hand, the ability of galectin-7 to interfere with the TGFβ/Smad pathway clearly differs from that of galectin-3, which is elevated in human liver fibrosis and which has been shown to be essential for TGFβ–mediated myofibroblast activation and matrix production (78). Thus, while induction of galectin-7 (or galectin-1) expression may prevent hepatic injury, galectin-3 expression must be repressed in order to develop a galectin-based therapeutic approach to the prevention and treatment of liver fibrosis. In cancer, however, this ability of galectin-7 to interfere with Smad2/3-mediated functions may explain, at least in part, its ability to promote cancer progression, because inhibition of Smad3 in mice promotes tumorigenesis (79)

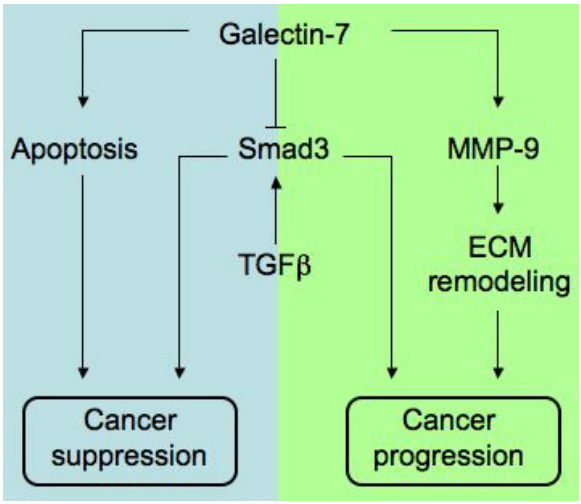

Figure 1. Dual roles of galectin-7 in suppressing and promoting tumor growth. In cancer, the effect of galectin-7 response is highly contextual. *De novo* expression of galectin-7 by p53 is associated with apoptosis, thereby inhibiting tumor growth. Alternatively, galectin-7 may modulate cancer progression by interfering with Smad3. Smad3 is a key regulatory protein in the TGFb signaling pathway, which is known to exert both tumor-suppressive and tumor promoting effects. Paradoxically, galectin-7 may also induces expression of genes that promote cancer progression, including MMP-9, thereby modulating microenvironment modification that cancer cells may exploit to their advantage. In this case, galectin-7 expression could be induced by NF-κB, a gene known to be expressed in highly aggressive tumor cells and a positive regulator of MMP-9. Such link between NF-κB and galectin-7 in cancer progression has been suggested by recent gene pathway profiling of a murine breast cancer model. Consequently, therapeutic applications that target galectin-7 needs to be refined by minimizing its protumor functions.

6. CONCLUDING REMARKS

In addition to sharing several structural features with other members of the galectin family, galectin-7 shares several common functional characteristics. For example, like other members of the galectin family, galectin-7 is characterized by the following: 1) it is found in both the cytoplasm and the nucleus of several cell types; 2) its expression is regulated by DNA methylation, 3) it can positively and negatively modulate apoptosis; and 4) it can favor or suppress cancer cell growth. However, beyond these commonly shared properties, there are an increasing number of indications that galectin-7 may have unique properties, most notably regarding its cellular distribution in specific tissues and its apparent preference for intracellular compartments. If galectin-7 expression is indeed restricted to the cytoplasm and the nucleus, its biological functions may be different from what we originally thought. Although glycosylated proteins are present intracellularly, functional roles by galectin-7 that are independent of its CRD should also be investigated, especially after recent reports on the associations between galectin-7 and specific transcription factors. It is likely that galectin-7 may, in turn, induce the expression of genes essential for tumor invasion and resistance to apoptosis, given its role in inducing MMP genes and its physical interactions with transcription factors (Figure .1). Future structure-function studies with mutated forms of galectin-7 will help clarify this issue. At the same time, a better characterization of the molecular mechanisms regulating its expression in normal and cancer cells is needed to better understand how galectin-7, originally identified as a p53-induced gene, is highly expressed in some cancer cells, promoting their survival, while promoting cell death in other cell types.

7. ACKNOWLEDGEMENTS

We would like to thank members or our laboratories for their contributions to the work cited in this review. This work was supported by the Canadian Institutes for Health Research. C.G.C. is supported by the CIHR. A.A.G. is supported by the Fondation Sybilla Hesse.

8. REFERENCES

1. Barondes SH, Castronovo V, Cooper DN, Cummings RD, Drickamer K, Feizi T, et al: Galectins: a family of animal beta-galactoside-binding lectins. *Cell* 76, 597-8 (1994)

2. Barondes SH, Cooper DN, Gitt MA, Leffler H: Galectins. Structure and function of a large family of animal lectins. *J Biol Chem* 269, 20807-10 (1994)

3. Yang RY, Rabinovich GA, Liu FT: Galectins: structure, function and therapeutic potential. *Expert Rev Mol Med* 10:e17 (2008)

4. Lobsanov YD, Gitt MA, Leffler H, Barondes SH, Rini JM: X-ray crystal structure of the human dimeric S-Lac lectin, L-14-II, in complex with lactose at 2.9-A resolution. *J Biol Chem* 268, 27034-8 (1993)

5. Seetharaman J, Kanigsberg A, Slaaby R, Leffler H, Barondes SH, Rini JM: X-ray crystal structure of the human galectin-3 carbohydrate recognition domain at 2.1-A resolution. *J Biol Chem* 273, 13047-52 (1998)

6. Barboni EA, Bawumia S, Henrick K, Hughes RC: Molecular modeling and mutagenesis studies of the N-terminal domains of galectin-3: evidence for participation with the C-terminal carbohydrate recognition domain in oligosaccharide binding. *Glycobiology* 10, 1201-8 (2000)

7. Ochieng J, Furtak V, Lukyanov P: Extracellular functions of galectin-3. Glycoconj J 19, 527-35 (2004)

8. Ackerman SJ, Liu L, Kwatia MA, Savage MP, Leonidas DD, Swaminathan GJ, et al: Charcot-Leyden crystal protein (galectin-10) is not a dual function galectin with lysophospholipase activity but binds a lysophospholipase inhibitor in a novel structural fashion. *J Biol Chem* 277, 14859-68 (2002)

9. Kubach J, Lutter P, Bopp T, Stoll S, Becker C, Huter E, et al: Human CD4+CD25+ regulatory T cells: proteome analysis identifies galectin-10 as a novel marker essential for their anergy and suppressive function. *Blood* 110, 1550-8 (2007)

10. Madsen P, Rasmussen HH, Flint T, Gromov P, Kruse TA, Honore B, et al: Cloning, expression, and chromosome mapping of human galectin-7. *J Biol Chem* 270, 5823-9 (1995)

11. Leonidas DD, Vatzaki EH, Vorum H, Celis JE, Madsen P, Acharya KR: Structural basis for the recognition of carbohydrates by human galectin-7. *Biochemistry* 37, 13930-40 (1998)

12. Kopitz J, Andre S, von Reitzenstein C, Versluis K, Kaltner H, Pieters RJ, et al: Homodimeric galectin-7 (p53-induced gene 1) is a negative growth regulator for human neuroblastoma cells. *Oncogene* 22, 6277-88 (2003)

13. Magnaldo T, Fowlis D, Darmon M: Galectin-7, a marker of all types of stratified epithelia. *Differentiation* 63, 159-68 (1998)

14. Sato M, Nishi N, Shoji H, Kumagai M, Imaizumi T, Hata Y, et al: Quantification of galectin-7 and its localization in adult mouse tissues. *J Biochem* 131, 255-60 (2002)

15. Demers M, Rose AA, Grosset AA, Biron-Pain K, Gaboury L, Siegel PM, et al: Overexpression of galectin-7, a myoepithelial cell marker, enhances spontaneous metastasis of breast cancer cells. *Am J Pathol* 176, 3023-31 (2010)

16. Nio J, Takahashi-Iwanaga H, Morimatsu M, Kon Y, Iwanaga T: Immunohistochemical and in situ hybridization analysis of galectin-3, a beta-galactoside binding lectin, in the urinary system of adult mice. *Histochem Cell Biol* 126, 45-56 (2006)

17. Nio-Kobayashi J, Takahashi-Iwanaga H, Iwanaga T: Immunohistochemical localization of six galectin subtypes in the mouse digestive tract. *J Histochem Cytochem* ;57, 41-50 (2009)

18. Moisan S, Demers M, Mercier J, Magnaldo T, Potworowski EF, St-Pierre Y: Upregulation of galectin-7 in murine lymphoma cells is associated with progression toward an aggressive phenotype. *Leukemia* 17:751-9 (2003)

19. Demers M, Magnaldo T, St-Pierre Y: A novel function for galectin-7: promoting tumorigenesis by up-regulating MMP-9 gene expression. *Cancer Res* 65, 5205-10 (2005)

20. Salvatore P, Benvenuto G, Caporaso M, Bruni CB, Chiariotti L: High resolution methylation analysis of the galectin-1 gene promoter region in expressing and nonexpressing tissues. *FEBS Lett* 421, 152-8 (1998)

21. Benvenuto G, Carpentieri ML, Salvatore P, Cindolo L, Bruni CB, Chiariotti L: Cell-specific transcriptional regulation and reactivation of galectin-1 gene expression are controlled by DNA methylation of the promoter region. *Mol Cell Biol* 16, 2736-43 (1996)

22. Salvatore P, Benvenuto G, Pero R, Lembo F, Bruni CB, Chiariotti L: Galectin-1 gene expression and methylation state in human T leukemia cell lines. *Int J Oncol ;*17, 1015-8 (2000)

23. Ruebel KH, Jin L, Qian X, Scheithauer BW, Kovacs K, Nakamura N, et al: Effects of DNA methylation on galectin-3 expression in pituitary tumors. *Cancer Res* 65, 1136-40 (2005)

24. Demers M, Couillard J, Giglia-Mari G, Magnaldo T, St-Pierre Y: Increased galectin-7 gene expression in lymphoma cells is under the control of DNA methylation. *Biochem Biophys Res Commun* 387, 425-9 (2009)

25. Dannenberg LO, Edenberg HJ: Epigenetics of gene expression in human hepatoma cells: expression profiling the response to inhibition of DNA methylation and histone deacetylation. *BMC Genomics* 7:181 (2006)

26. Vallender TW, Lahn BT: Localized methylation in the key regulator gene endothelin-1 is associated with cell type-specific transcriptional silencing. *FEBS Lett* 580, 4560-6 (2006)

27. Mueller W, Nutt CL, Ehrich M, Riemenschneider MJ, von Deimling A, van den Boom D, et al: Downregulation of RUNX3 and TES by hypermethylation in glioblastoma. *Oncogene* 26, 583-93 (2007)

28. Polyak K, Xia Y, Zweier JL, Kinzler KW, Vogelstein B: A model for p53-induced apoptosis. *Nature* 389, 300-5 (1997)

29. Koster MI, Kim S, Roop DR: p63 deficiency: a failure of lineage commitment or stem cell maintenance? *J Investig Dermatol Symp Proc* 10, 118-23 (2005)

30. Demers M, Rose AA, Grosset AA, Biron-Pain K, Gaboury L, Siegel PM, et al: Overexpression of galectin-7, a myoepithelial cell marker, enhances spontaneous metastasis of breast cancer cells. *Am J Pathol* 176, 3023-31 (2010)

31. Karin M: NF-kappaB and cancer: mechanisms and targets. *Mol Carcinog* 45, 355-61 (2006)

32. Bemmo A, Dias C, Rose AA, Russo C, Siegel P, Majewski J: Exon-level transcriptome profiling in murine breast cancer reveals splicing changes specific to tumors with different metastatic abilities. *PLoS One* 5, e11981 (2010)

33. Harrison FL, Wilson TJ: The 14 kDa beta-galactoside binding lectin in myoblast and myotube cultures: localization by confocal microscopy. *J Cell Sci* 101, 635-46 (1992)

34. Thery C, Boussac M, Veron P, Ricciardi-Castagnoli P, Raposo G, Garin J, et al: Proteomic analysis of dendritic cell-derived exosomes: a secreted subcellular compartment distinct from apoptotic vesicles. *J Immunol* 166, 7309-18 (2001)

35. Keryer-Bibens C, Pioche-Durieu C, Villemant C, Souquere S, Nishi N, Hirashima M, et al: Exosomes released by EBV-infected nasopharyngeal carcinoma cells convey the viral latent membrane protein 1 and the immunomodulatory protein galectin 9. *BMC Cancer* 6:283 (2006)

36. Iurisci I, Tinari N, Natoli C, Angelucci D, Cianchetti E, Iacobelli S: Concentrations of galectin-3 in the sera of normal controls and cancer patients. *Clin Cancer Res* 6, 1389-93 (2000)

37. Saussez S, Glinoer D, Chantrain G, Pattou F, Carnaille B, Andre S, et al: Serum galectin-1 and galectin-3 levels in benign and malignant nodular thyroid disease. *Thyroid* 18, 705-12 (2008)

38. Saussez S, Lorfevre F, Lequeux T, Laurent G, Chantrain G, Vertongen F, et al : The determination of the levels of circulating galectin-1 and -3 in HNSCC patients could be used to monitor tumor progression and/or responses to therapy. *Oral Oncol* 44, 86-93 (2008)

39. He J, Baum LG: Endothelial cell expression of galectin-1 induced by prostate cancer cells inhibits T-cell transendothelial migration. *Lab Invest* 86, 578-90 (2006)

40. Tsai CM, Chiu YK, Hsu TL, Lin IY, Hsieh SL, Lin KI: Galectin-1 promotes immunoglobulin production during plasma cell differentiation. *J Immunol* 181, 4570-9 (2008)

41. Motran CC, Molinder KM, Liu SD, Poirier F, Miceli MC: Galectin-1 functions as a Th2 cytokine that selectively induces Th1 apoptosis and promotes Th2 function. *Eur J Immunol* 38, 3015-27 (2008)

42. Gieseke F, Bohringer J, Bussolari R, Dominici M, Handgretinger R, Muller I: Human multipotent mesenchymal stromal cells use galectin-1 to inhibit immune effector cells. *Blood* 116, 3770-9 (2010)

43. Garner OB, Baum LG: Galectin-glycan lattices regulate cell-surface glycoprotein organization and signalling. *Biochem Soc Trans* 36, 1472-7 (2008)

44. Partridge EA, Le Roy C, Di Guglielmo GM, Pawling J, Cheung P, Granovsky M, et al: Regulation of cytokine receptors by Golgi N-glycan processing and endocytosis. *Science* 306, 120-4 (2004)

45. Saussez S, Decaestecker C, Lorfevre F, Chevalier D, Mortuaire G, Kaltner H, et al: Increased expression and altered intracellular distribution of adhesion/growth-regulatory lectins galectins-1 and -7 during tumour progression in hypopharyngeal and laryngeal squamous cell carcinomas. *Histopathology* 52, 483-93 (2008)

46. Kuwabara I, Kuwabara Y, Yang RY, Schuler M, Green DR, Zuraw BL, et al: Galectin-7 (PIG1) exhibits pro-apoptotic function through JNK activation and mitochondrial cytochrome c release. *J Biol Chem* 277, 3487-97 (2002)

47. Timmons PM, Colnot C, Cail I, Poirier F, Magnaldo T: Expression of galectin-7 during epithelial development coincides with the onset of stratification. *Int J Dev Biol* 43, 229-35 (1999)

48. Bernerd F, Sarasin A, Magnaldo T: Galectin-7 overexpression is associated with the apoptotic process in UVB-induced sunburn keratinocytes. *Proc Natl Acad Sci U S A* 96, 11329-34 (1999)

49. Cao Z, Said N, Amin S, Wu HK, Bruce A, Garate M, et al: Galectins-3 and -7, but not galectin-1, play a role in re-epithelialization of wounds. *J Biol Chem* 277, 42299-305 (2002)

50. Cao Z, Wu HK, Bruce A, Wollenberg K, Panjwani N: Detection of differentially expressed genes in healing mouse corneas, using cDNA microarrays. *Invest Ophthalmol Vis Sci* 43, 2897-904 (2002)

51. Cao Z, Said N, Wu HK, Kuwabara I, Liu FT, Panjwani N: Galectin-7 as a potential mediator of corneal epithelial cell migration. *Arch Ophthalmol* 121, 82-6 (2003)

52. Gendronneau G, Sidhu SS, Delacour D, Dang T, Calonne C, Houzelstein D, et al: Galectin-7 in the control of epidermal homeostasis after injury. *Mol Biol Cell* 19, 5541-9 (2008)

53. Ueda S, Kuwabara I, Liu FT: Suppression of tumor growth by galectin-7 gene transfer. *Cancer Res* 64, 5672-6 (2004)

54. Liu FT, Rabinovich GA: Galectins as modulators of tumour progression. *Nat Rev Cancer* 5, 29-41 (2005)

55. Brewer CF: Thermodynamic binding studies of galectin-1, -3 and -7. *Glycoconj J* 19, 459-65 (2004)

56. Lu J, Pei H, Kaeck M, Thompson HJ: Gene expression changes associated with chemically induced rat mammary carcinogenesis. *Mol Carcinog* 20, 204-15 (1997)

57. Antoine E, Pauwels C, Verrelle P, Lascaux V, Poupon MF: In vivo emergence of a highly metastatic tumour cell line from a rat rhabdomyosarcoma after treatment with an alkylating agent. *Br J Cancer* 57, 469-74 (1988)

58. McElroy MK, Kaushal S, Tran Cao HS, Moossa AR, Talamini MA, Hoffman RM, et al: Upregulation of thrombospondin-1 and angiogenesis in an aggressive human pancreatic cancer cell line selected for high metastasis. *Mol Cancer Ther* 8, 1779-86 (2009)

59. Demers M, Biron-Pain K, Hebert J, Lamarre A, Magnaldo T, St-Pierre Y: Galectin-7 in lymphoma: elevated expression in human lymphoid malignancies and decreased lymphoma dissemination by antisense strategies in experimental model. *Cancer Res* ;67, 2824-9 (2007)

60. Nakahara S, Oka N, Raz A: On the role of galectin-3 in cancer apoptosis. *Apoptosis* 10, 267-75 (2005)

61. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al: Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 98, 10869-74 (2001)

62. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, et al: Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Natl Acad Sci U S A* 100, 8418-23 (2003)

63. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al: Molecular portraits of human breast tumours. *Nature* 406, 747-52 (2000)

64. Fan C, Oh DS, Wessels L, Weigelt B, Nuyten DS, Nobel AB, et al: Concordance among gene-expression-based predictors for breast cancer. *N Engl J Med* 355, 560-9 (2006)

65. Mackay A, Jones C, Dexter T, Silva RL, Bulmer K, Jones A, et al: cDNA microarray analysis of genes associated with ERBB2 (HER2/neu) overexpression in human mammary luminal epithelial cells. *Oncogene* 22, 2680-8 (2003)

66. Castronovo V, Van Den Brule FA, Jackers P, Clausse N, Liu FT, Gillet C, et al: Decreased expression of galectin-3 is associated with progression of human breast cancer. *J Pathol* 179, 43-8 (1996)

67. Rakha EA, El-Sayed ME, Reis-Filho J, Ellis IO: Patho-biological aspects of basal-like breast cancer. *Breast Cancer Res Treat* 113, 411-22 (2009)

68. Gusterson B: Do 'basal-like' breast cancers really exist? *Nat Rev Cancer* 9, 128-34 (2009)

69. Asselin-Labat ML, Sutherland KD, Barker H, Thomas R, Shackleton M, Forrest NC, et al: Gata-3 is an essential regulator of mammary-gland morphogenesis and luminal-cell differentiation. *Nat Cell Biol* 9, 201-9 (2007)

70. Jones C, Mackay A, Grigoriadis A, Cossu A, Reis-Filho JS, Fulford L, et al: Expression profiling of purified normal human luminal and myoepithelial breast cells: identification of novel prognostic markers for breast cancer. *Cancer Res* 64, 3037-45 (2004)

71. Kunigal S, Lakka SS, Gondi CS, Estes N, Rao JS: RNAi-mediated downregulation of urokinase plasminogen activator receptor and matrix metalloprotease-9 in human breast cancer cells results in decreased tumor invasion, angiogenesis and growth. *Int J Cancer* 121, 2307-16 (2007)

72. Safina A, Vandette E, Bakin AV: ALK5 promotes tumor angiogenesis by upregulating matrix metalloproteinase-9 in tumor cells. *Oncogene* 26, 2407-22 (2007)

73. Hikita C, Vijayakumar S, Takito J, Erdjument-Bromage H, Tempst P, Al-Awqati Q: Induction of terminal differentiation in epithelial cells requires polymerization of hensin by galectin 3. *J Cell Biol* 151, 1235-46 (2000)

74. Hittelet A, Legendre H, Nagy N, Bronckart Y, Pector JC, Salmon I, et al: Upregulation of galectins-1 and -3 in human colon cancer and their role in regulating cell migration. *Int J Cancer* 103, 370-9 (2003)

75. Moiseeva EP, Williams B, Goodall AH, Samani NJ: Galectin-1 interacts with beta-1 subunit of integrin. *Biochem Biophys Res Commun* 310, 1010-6 (2003)

76. Inagaki Y, Higashi K, Kushida M, Hong YY, Nakao S, Higashiyama R, et al: Hepatocyte growth factor suppresses profibrogenic signal transduction via nuclear export of Smad3 with galectin-7. *Gastroenterology* 134, 1180-90 (2008)

77. Okano K, Uchida K, Nitta K, Hayashida T: Galectin-1 suppresses alpha2(I) collagen through Smad3 in renal epithelial cells. *Cell Mol Life Sci* 65, 3304-11 (2008)

78. Henderson NC, Mackinnon AC, Farnworth SL, Poirier F, Russo FP, Iredale JP, et al: Galectin-3 regulates myofibroblast activation and hepatic fibrosis. *Proc Natl Acad Sci U S A* 103, 5060-5 (2006)

79. Zhu Y, Richardson JA, Parada LF, Graff JM: Smad3 mutant mice develop metastatic colorectal cancer. *Cell* 94, 703-14 (1998)

80. www.proteinatlas.org.

81. Rendl M, Lewis L, Fuchs E: Molecular dissection of mesenchymal-epithelial interactions in the hair follicle. *PLoS Biol* 3, e331 (2005)

82. Marra M, Hillier L, Allen M, Bowles M, Dietrich N, Dubuque T, Geisel S, KucabaT, Lacy M, Le M, Martin J, Morris M, Schellenberg K, Steptoe M, Tan F, Underwood K, Moore B, Theising B, Wylie T, Lennon G, Soares B, Wilson R, Waterston R: The WashU-HHMI Mouse EST Project. GDS868 record. http://www.ncbi.nlm.nih.gov/geoprofiles/

83. Lohr M, Lensch M, Andre S, Kaltner H, Siebert HC, Smetana K, Jr., et al: Murine homodimeric adhesion/growth-regulatory galectins-1, -2 and -7: comparative profiling of gene/ promoter sequences by database mining, of expression by RT-PCR/immunohistochemistry and of contact sites for carbohydrate ligands by computational chemistry. *Folia Biol (Praha)* 53, 109-28 (2007)

84. Langbein S, Brade J, Badawi JK, Hatzinger M, Kaltner H, Lensch M, et al: Gene-expression signature of adhesion/growth-regulatory tissue lectins (galectins) in transitional cell cancer and its prognostic relevance. *Histopathology* 51, 681-90 (2007)

85. Klattig J, Sierig R, Kruspe D, Besenbeck B, Englert C: Wilms' Tumor Protein Wt1 Is an Activator of the Anti-Mullerian Hormone Receptor Gene Amhr2. *Mol Cell Biol* 27, 4355-64 (2007)

86. Zhu X, Ding M, Yu ML, Feng MX, Tan LJ, Zhao FK: Identification of galectin-7 as a potential biomarker for esophageal squamous cell carcinoma by proteomic analysis. *BMC Cancer* 10, 290 (2010)

87. Nio J, Kon Y, Iwanaga T: Differential Cellular Expression of Galectin Family mRNAs in the Epithelial Cells of the Mouse Digestive Tract. *J Histochem Cytochem* 53, 1323-34 (2005)

88. Young PP, Modur V, Teleron AA, Ladenson JH: Enrichment of Genes in the Aortic Intima That Are Associated With Stratified Epithelium: Implications of Underlying Biomechanical and Barrier Properties of the Arterial Intima. *Circulation* 111, 2382-90 (2005)

89. Elvidge GP, Glenny L, Appelhoff RJ, Ratcliffe PJ, Ragoussis J, Gleadle JM: Concordant regulation of gene expression by hypoxia and 2-oxoglutarate-dependent dioxygenase inhibition: the role of HIF-1alpha, HIF-2alpha, and other pathways. *J Biol Chem* 281, 15215-26 (2006)

90. Koster MI, Kim S, Huang J, Williams T, Roop DR: TAp63alpha induces AP-2gamma as an early event in epidermal morphogenesis. *Dev Biol* 289, 253-61 (2006)

91. Lucerna M, Pomyje J, Mechtcheriakova D, Kadl A, Gruber F, Bilban M, et al: Sustained expression of early growth response protein-1 blocks angiogenesis and tumor growth. *Cancer Res* 66, 6708-13 (2006)

92. Richardson GD, Bazzi H, Fantauzzo KA, Waters JM, Crawford H, Hynd P, et al: KGF and EGF signalling block hair follicle induction and promote interfollicular epidermal fate in developing mouse skin. *Development* 136, 2153-64 (2009)

93. Hanson JL, Hawke NA, Kashatus D, Baldwin AS: The nuclear factor kappaB subunits RelA/p65 and c-Rel potentiate but are not required for Ras-induced cellular transformation. *Cancer Res* 64, 7248-55 (2004)

94. Carroll JS, Meyer CA, Song J, Li W, Geistlinger TR, Eeckhoute J, et al: Genome-wide analysis of estrogen receptor binding sites. *Nat Genet* 38, 1289-97 (2006)

95. Zhang J, Smolen GA, Haber DA: Negative regulation of YAP by LATS1 underscores evolutionary conservation of the Drosophila Hippo pathway. *Cancer Res* 68, 2789-94 (2008)

96. Wu W, Zou M, Brickley DR, Pew T, Conzen SD: Glucocorticoid receptor activation signals through forkhead transcription factor 3a in breast cancer cells. *Mol Endocrinol* 20, 2304-14 (2006)

97. Guo S, Lu J, Subramanian A, Sonenshein GE: Microarray-assisted pathway analysis identifies mitogen-activated protein kinase signaling as a mediator of resistance to the green tea polyphenol epigallocatechin 3-gallate in her-2/neu-overexpressing breast cancer cells. *Cancer Res* 66, 5322-9 (2006)

98. Landis MD, Seachrist DD, Abdul-Karim FW, Keri RA: Sustained trophism of the mammary gland is sufficient to accelerate and synchronize development of ErbB2/Neu-induced tumors. *Oncogene* 25, 3325-34 (2006)

99. Chang TC, Wentzel EA, Kent OA, Ramachandran K, Mullendore M, Lee KH, et al: Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. *Mol Cell* 26, 745-52 (2007)

100. Magnaldo T, Bernerd F, Darmon M: Galectin-7, a human 14-kDa S-lectin, specifically expressed in keratinocytes and sensitive to retinoic acid. *Dev Biol* 168, 259-71 (1995)

101. Chan MM, Lu X, Merchant FM, Iglehart JD, Miron PL: Gene expression profiling of NMU-induced rat mammary tumors: cross species comparison with human breast cancer. *Carcinogenesis* 26, 1343-53 (2005)

102. Lin KY, Lu D, Hung CF, Peng S, Huang L, Jie C, et al: Ectopic expression of vascular cell adhesion molecule-1 as a new mechanism for tumor immune evasion. *Cancer Res* 67, 1832-41 (2007)

103. Matsui Y, Ueda S, Watanabe J, Kuwabara I, Ogawa O, Nishiyama H: Sensitizing effect of galectin-7 in urothelial cancer to cisplatin through the accumulation of intracellular reactive oxygen species. *Cancer Res* 67, 1212-20 (2007)

104. Liu H, Knabb JR, Spike BT, Macleod KF: Elevated poly-(ADP-ribose)-polymerase activity sensitizes retinoblastoma-deficient cells to DNA damage-induced necrosis. *Mol Cancer Res* 7, 1099-109 (2009)

105. Troester MA, Hoadley KA, Sorlie T, Herbert BS, Borresen-Dale AL, Lonning PE, et al: Cell-type-specific responses to chemotherapeutics in breast cancer. *Cancer Res* 64, 4218-26 (2004)

106. Troester MA, Hoadley KA, Parker JS, Perou CM: Prediction of toxicant-specific gene expression signatures after chemotherapeutic treatment of breast cell lines. *Environ Health Perspect* 112, 1607-13 (2004)

107. Saussez S, Nonclercq D, Laurent G, Wattiez R, Andre S, Kaltner H, et al: Toward functional glycomics by localization of tissue lectins: immunohistochemical galectin fingerprinting during diethylstilbestrol-induced kidney tumorigenesis in male Syrian hamster. *Histochem Cell Biol* 123, 29-41 (2005)

108. Shen J, Riggs PK, Hensley SC, Schroeder LJ, Traner AR, Kochan KJ, et al: Differential expression of multiple anti-apoptotic proteins in epidermis of IGF-1 transgenic mice as revealed by 2-dimensional gel electrophoresis/mass spectrometry analysis. *Mol Carcinog* 46, 331-40 (2007)

109. Demers Ml, Biron-Pain K, HÃ©bert Je, Lamarre A, Magnaldo T, St-Pierre Y: Galectin-7 in Lymphoma: Elevated Expression in Human Lymphoid Malignancies and Decreased Lymphoma Dissemination by Antisense Strategies in Experimental Model. *Cancer Research* 67, 2824-9 (2007)

110. Critchley-Thorne RJ, Yan N, Nacu S, Weber J, Holmes SP, Lee PP: Down-regulation of the interferon signaling pathway in T lymphocytes from patients with metastatic melanoma. *PLoS Med* 4, e176 (2007)

111. Lu J, Pei H, Kaeck M, Thompson HJ: Gene expression changes associated with chemically induced rat mammary carcinogenesis. *Molecular Carcinogenesis* 20, 204-15 (1997)

112. Cada Z, Chovanec M, Smetana K, Betka J, Lacina L, Plzak J, et al: Galectin-7: will the lectin's activity establish clinical correlations in head and neck squamous cell and basal cell carcinomas? *Histol Histopathol* 24, 41-8 (2009)

113. Riker AI, Enkemann SA, Fodstad O, Liu S, Ren S, Morris C, et al: The gene expression profiles of primary and metastatic melanoma yields a transition point of tumor progression and metastasis. *BMC Med Genomics* 1, 13 (2008)

114. Smith AP, Hoek K, Becker D: Whole-genome expression profiling of the melanoma progression pathway reveals marked molecular differences between nevi/melanoma in situ and advanced-stage melanomas. *Cancer Biol Ther* 4, 1018-29 (2005)

115. Talantov D, Mazumder A, Yu JX, Briggs T, Jiang Y, Backus J, et al: Novel Genes Associated with Malignant Melanoma but not Benign Melanocytic Lesions. *Clinical Cancer Research* 11, 7234-42 (2005)

116. Zhu H, Pei H-p, Zeng S, Chen J, Shen L-f, Zhong M-z, et al: Profiling Protein Markers Associated with the Sensitivity to Concurrent Chemoradiotherapy in Human Cervical Carcinoma. *Journal of Proteome Research* 8, 3969-76 (2009)

117. Park JE, Chang WY, Cho M: Induction of matrix metalloproteinase-9 by galectin-7 through p38 MAPK signaling in HeLa human cervical epithelial adenocarcinoma cells. *Oncol Rep* 22, 1373-9 (2009)

118. Shadeo A, Chari R, Vatcher G, Campbell J, Lonergan KM, Matisic J, et al: Comprehensive serial analysis of gene expression of the cervical transcriptome. *BMC Genomics* 8, 142 (2007)

119. Scotto L, Narayan G, Nandula SV, Arias-Pulido H, Subramaniyam S, Schneider A, et al: Identification of copy number gain and overexpressed genes on chromosome arm 20q by an integrative genomic approach in cervical cancer: Potential role in progression. *Genes, Chromosomes and Cancer* 47, 755-65 (2008)

120. Rorive S, Eddafali B, Fernandez S, Decaestecker C, Andre S, Kaltner H, et al: Changes in galectin-7 and cytokeratin-19 expression during the progression of malignancy in thyroid tumors: diagnostic and biological implications. *Mod Pathol* 15, 1294-301 (2002)

121. Than TH, Swethadri GK, Wong J, Ahmad T, Jamil D, Maganlal RK, et al: Expression of Galectin-3 and Galectin-7 in thyroid malignancy as potential diagnostic indicators. *Singapore Med J* 49, 333-8 (2008)

122. Saussez S, Cludts S, Capouillez A, Mortuaire G, Smetana K, Jr., Kaltner H, et al: Identification of matrix metalloproteinase-9 as an independent prognostic marker in laryngeal and hypopharyngeal cancer with opposite correlations to adhesion/growth-regulatory galectins-1 and -7. *Int J Oncol* 34, 433-9 (2009)

123. Saussez S, Cucu D-R, Decaestecker C, Chevalier D, Kaltner H, André S, et al: Galectin 7 (p53-Induced Gene 1): A New Prognostic Predictor of Recurrence and Survival in Stage IV Hypopharyngeal Cancer. *Annals of Surgical Oncology* 13, 999-1009 (2006)

124. Wachi S, Yoneda K, Wu R: Interactome-transcriptome analysis reveals the high centrality of genes differentially expressed in lung cancer tissues. *Bioinformatics* 21, 4205-8 (2005)

125. Kuner R, Muley T, Meister M, Ruschhaupt M, Buness A, Xu EC, et al: Global gene expression analysis reveals specific patterns of cell junctions in non-small cell lung cancer subtypes. *Lung Cancer* 63, 32-8 (2009)

126. Daniel VC, Marchionni L, Hierman JS, Rhodes JT, Devereux WL, Rudin CM, et al: A Primary Xenograft Model of Small-Cell Lung Cancer Reveals Irreversible Changes in Gene Expression Imposed by Culture In vitro. *Cancer Research* 69, 3364-73 (2009)

127. Ueda S, Kuwabara I, Liu F-T: Suppression of Tumor Growth by Galectin-7 Gene Transfer. *Cancer Research* 64, 5672-6 (2004)

128. Chen J, He Q-Y, Yuen AP-W, Chiu J-F: Proteomics of buccal squamous cell carcinoma: The involvement of multiple pathways in tumorigenesis. *PROTEOMICS* 4, 2465-75 (2004)

129. Matsui Y, Ueda S, Watanabe J, Kuwabara I, Ogawa O, Nishiyama H: Sensitizing Effect of Galectin-7 in Urothelial Cancer to Cisplatin through the Accumulation of Intracellular Reactive Oxygen Species. *Cancer Research* 67, 1212-20 (2007)

130. Ostergaard M, Rasmussen HH, Nielsen HV, Vorum H, Orntoft TF, Wolf H, et al: Proteome profiling of bladder squamous cell carcinomas: identification of markers that define their degree of differentiation. *Cancer Res* 57, 4111-7 (1997)

131. Cornelissen M, van der Kuyl AC, van den Burg R, Zorgdrager F, van Noesel CJ, Goudsmit J: Gene expression profile of AIDS-related Kaposi's sarcoma. *BMC Cancer* 3, 7 (2003)

Key Words: Galectins, Apoptosis, Mammary Cancer, Mammary Myoepithelial Cells, p53, Review

Send correspondence to: Yves St-Pierre, INRS-Institut Armand-Frappier, 531 Boul. des Prairies, Laval, Quebec, Canada H7V1B7, Tel: 450-686-5354, Fax: 450-686-5501, E-mail: yves.st-pierre@iaf.inrs.ca

http://www.bioscience.org/current/vol17.htm