Galectin-7 in Lymphoma: Elevated Expression in Human Lymphoid Malignancies and Decreased Lymphoma Dissemination by Antisense Strategies in Experimental Model

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Abstract

Galectin-7 is found mainly in stratified squamous epithelia as well as in various other types of cancer cells. As with other members of the galectin family, the expression of galectin-7 has been shown to negatively regulate the development of some tumors while correlating with the progression of other tumor types. For example, up-regulation of galectin-7 is associated with rat mammary carcinomas and with progression to T-cell malignancy. Here, we provide evidence indicating that galectin-7 functions as an important molecule in the dissemination of lymphoma cells in vivo. We found that stable transfection of lymphoma cells with a plasmid encoding antisense galectin-7 cDNA significantly inhibited the dissemination and invasion of lymphoma cells to peripheral organs, thereby increasing the survival of mice. We also found that inhibition of galectin-7 in aggressive lymphoma cells correlated with a decreased invasion of tumor cells in target organs and a reduced expression of matrix metalloproteinase-9, a gene associated with a poor prognosis in non–Hodgkin’s lymphoma. We finally examined the expression of galectin-7 in 50 specimens of different mature B-cell neoplasms and found high galectin-7 expression levels in a significant proportion of mature B-cell neoplasms but not in normal B cells. Taken together, these findings suggest that galectin-7 is a potential therapeutic target in the treatment of lymphoid malignancies.

Introduction

Galectins constitute a family of animal lectins defined by shared consensus amino acid sequences and affinity for β-galactose–containing oligosaccharides (1). Members of the galectin family contain carbohydrate recognition domains of ~130 amino acids, which are involved in β-galactoside binding (2–4). Some galectins are secreted by the cell, probably through a nonclassic secretory pathway, because all members do not have a signal sequence, which would be required for protein secretion through the classic secretory pathway. Thus, galectins, including galectin-1 and galectin-7, can be found in the extracellular space. Their ability to bind and cross-link to cell surface glycoconjugates, some of which are transmembrane proteins, can thus trigger a cascade of transmembrane signaling events (5–8).

In mammals, the distribution of galectins is tissue specific and their expression is developmentally regulated (1, 9). They play an important role in several physiologic processes, including embryonic development, wound healing, apoptosis, intercellular adhesion, cell migration, and immune response. They are also involved in several pathologic conditions, including infectious diseases and cancer. For example, galectin-1 and galectin-9 can induce tumor cell apoptosis when added exogenously to the cell, whereas galectin-7 and galectin-12 promote apoptosis through intracellular mechanisms (10).

Galectin-7 was initially described as a marker of the differentiation levels of keratinocytes by Madsen et al. (11). At first glance, galectin-7 should aid in the elimination of tumor cells because its expression is induced by p53 and functions as a regulator of apoptosis. A series of recent studies have indicated, however, that expression of galectin-7 was associated with tumor progression. Lu et al. (12) have first reported that galectin-7 was overexpressed in rat mammary carcinomas induced by 7,12-dimethylbenz(a)anthracene. Rorive et al. (13) have subsequently observed that galectin-7 expression was markedly down-regulated in benign thyroid tumors compared with malignant ones. Using an approach based on genomic analysis of an aggressive lymphoma variant and its nonaggressive parental cells, we found that the most prominent change among the genes tested was the strong up-regulation of galectin-7 (14). Here, we used an antisense approach to provide evidence that decreased expression of galectin-7 in aggressive murine lymphoma cells inhibits their aggressive behavior in vivo. Furthermore, examination of samples from patients with different mature B-cell lymphoproliferative disorders shows for the first time that galectin-7 is expressed at high levels in lymphoid malignancies but not in normal lymphocytes. Our data suggest that galectin-7 may represent a potential target for lymphoma therapy.

Materials and Methods

Cell lines and reagents. The aggressive 16T2S11 (S11) lymphoma cell line was established from in vivo passages of the parental 16T2 cell line and has been described elsewhere (15). This aggressive lymphoma cell line expresses α(α)TcR, CD3e, TL, gp70, LFA-1, ICAM-1, and ICAM-2 and is maintained in culture without loss of aggressiveness (14, 15). Cells were maintained in RPMI 1640 complete medium [supplemented with 8% (v/v) FCS, 2 mmol/L L-glutamine, 10 mmol/L HEPES buffer, 0.1 unit/mL penicillin, 50 μg/mL streptomycin, and 55 μmol/L [β-mercaptoethanol]. All products were from Life Technologies (Burlington, Ontario, Canada). Horseradish peroxidase (HRP)-conjugated donkey anti-rabbit and anti-mouse secondary antibodies were obtained from Amersham Biosciences (Piscataway, NJ). The rabbit polyclonal antibody specific for galectin-7 has been described (16). The rabbit polyclonal antibody for galectin-1 was kindly provided by Dr. Brian Key (University of Queensland, Brisbane, Australia).
Control transfectants (galectin-1) are representative of three independent experiments. Recombinant mouse galectin-1 in all transfectants was not decreased in all transfectants tested. Data are the results. As an internal control, amplification of GAPDH or β-actin mRNA was carried out by reverse transcription-PCR (RT-PCR) using specific primers. Amplified products were analyzed by electrophoresis on 1.2% agarose gels using ethidium bromide staining and UV illumination. Loading was equalized to the internal control mRNA.

**Generation of stable transfectants expressing galectin-7 antisense.** To obtain stable S11 transfectants expressing galectin-7 antisense, the cDNA encoding the murine galectin-7 (20) was cloned in the antisense orientation in Srx eukaryotic expression vector (kindly provided by Dr. François Denis, INRS-Institut Armand-Frappier, Laval, Quebec, Canada) using SpeI and NotI restriction enzymes to excise the cDNA, the SpeI fragment was blunted, and the galectin-7 cDNA was inserted into Srx vector using NotI and EcoRV restriction enzyme. Controls were generated using S11 lymphoma cells transfected with the empty Srx vector alone. Transfection was carried out by electroporation (Gene Pulser, Bio-Rad Laboratories) and done using the following variables: 40 μg DNA per 10⁶ cells in PBS on ice, 960 μF, and 260 mV. After 48 h of culture in complete medium, transfected cells were allowed to grow in complete medium containing 2 μg/ml puromycin. Individual colonies were expanded, and PCR analysis was carried out on SDS-PAGE gel and transferred onto nitrocellulose membranes (Bio-Rad Laboratories, Mississauga, Ontario, Canada). Membranes were blocked with 10% milk in PBS/0.3% Tween 20 overnight and subsequently blotted for 2 h with primary antibodies. Membranes were probed with polyclonal rabbit anti-galectin-7 (1:1,000), rabbit anti-galectin-1 (1:1,000; refs. 17, 18), or mouse anti-β-actin antibodies. Secondary antibodies consisted of HRP-conjugated donkey anti-rabbit or anti-mouse IgG. Detection was done by the enhanced chemiluminescence method (Amersham Biosciences).

**Western blot analysis.** Cells and frozen tissues were homogenized and resuspended in lysis buffer [10 mmol/L Tris (pH 7.5), 2.5% Triton X-100] containing protease inhibitors (Roche, Laval, Quebec, Canada). Equal amounts of whole-cell (50 μg) or tissue (100 μg) extracts were separated on

**Figure 1. Inhibition of galectin-7 expression in antisense transfectants.** The aggressive S11 T lymphoma cells were transfected with the Srx/puro expression vector containing the murine galectin-7 antisense cDNA, and stable transfectants (S11G7AS) that do not express galectin-7 were obtained. Control transfectants (S11Sr) included lymphoma cells transfected with the Srx/puro expression vector without cDNA insert. Level of galectin-7 expression in the antisense transfectants was assessed by RT-PCR (A) and Western blot analysis (B) and found to be suppressed in all clones compared with those of the aggressive S11 cell lines and controls. Immunoblotting with β-actin was done as specificity control. Galectin-7 expression was not induced on long-term culture of the clones but was nevertheless always assessed by Western blot analysis before their in vivo testing. C, constitutive expression of galectin-1 in all transfectants was not decreased in all transfectants tested. Data are representative of three independent experiments. Recombinant mouse galectin-1 (mgal-1) was used as a positive control for immunoblotting.

Human specimens. Peripheral blood or bone marrow cells were obtained from patients with different mature B-cell lymphoproliferative diseases (LPD). These samples were collected by the Quebec Leukemia Cell Bank after informed consent. Morphology, immunophenotyping, and molecular cytogenetics of tumors were used as criteria to classify them according to the WHO classification of tumors (19). Fifty samples were analyzed: 31 chronic lymphocytic leukemias (CLL; including 1 case of transformed CLL), 2 B-cell prolymphocytic leukemias, 2 follicular lymphomas, 2 splenic marginal zone lymphomas, 5 mantle cell lymphomas, 1 lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, 2 Burkitt lymphomas, and 5 B-cell LPD not classified. As controls, purified CD19+ B cells were obtained from peripheral blood mononuclear cells from 10 healthy donors using magnetic cell sorting with CD19 microbeads (Miltenyi Biotec, Bergisch Gladbach, Germany) and the autoMACS separator (Miltenyi Biotec).

Western blot analysis. Cells and frozen tissues were homogenized and resuspended in lysis buffer [10 mmol/L Tris (pH 7.5), 2.5% Triton X-100] containing protease inhibitors (Roche, Laval, Quebec, Canada). Equal amounts of whole-cell (50 μg) or tissue (100 μg) extracts were separated on
Cell samples.

Magnification, shows severe infiltration in the cortex. Sections were stained with H&E.

vector for galectin-7 was milder in the kidney compared with the control, which

of two independent experiments carried out with two distinct clones. B, effect of

inhibition of galectin-7 on the infiltration of aggressive lymphoma cells in

peripheral organs. Histopathology of kidney showing the infiltration of control

lymphoma cells transfected with the antisense (S11Sr, right) or galectin-7 antisense (left) lymphoma cells found in the kidney. Magnification, ×400. Infiltration of lymphoma cells transfected with the antisense vector for galectin-7 was milder in the kidney compared with the control, which shows severe infiltration in the cortex. Sections were stained with HE.

peripheral DNA for assessing vector insertion. Galectin-7 expression was monitored by Western blot analysis.

Peripheral lymphoid tumor growth. Lymphoma cells (10^5) transfected with the empty vector (Sr) or with vectors encoding galectin-7 antisense were inoculated i.v. via the tail vein of 6- to 8-week-old C57BL/6 mice (5–10 mice per group). Animals were monitored periodically for clinical signs of lymphoid tumor growth: dyspnea, running, and splenomegaly. When moribund, mice were sacrificed, and spleen, liver, and kidneys were examined and collected at necropsy. Biopsy fragments were fixed in formaldehyde solution and stained for histology or processed for gene

Quantitative RT-PCR analyses. Quantitative RT-PCR analyses were carried out using the DyNAmo SYBR Green 2-Step qRT-PCR kit (New England Biolabs, Ipswich, MA). Briefly, total RNA (1 μg) was reverse transcribed using the Moloney murine leukemia virus reverse transcriptase (New England Biolabs). Real-time PCR was then done with a Rotor-Gene 3000 PCR cycler (Corbett Research, Sydney, New South Wales, Australia) using the following conditions: 40 cycles of 94°C/10 s, 64°C/30 s, and 72°C/ 30 s. The primers used for quantitative PCR amplification were 5'-TTGCTCCTGTGTTGAAAGCCAC-3' for sense human galectin-7 and 5'-AGGTTCATGTAACCTGCTGTC-3' for antisense. Galectin-7 dsDNA serial dilutions were used for establishing a standard curve ranging from 227 to 227,000 copy numbers. The results were analyzed using the Rotor-Gene 6 software. Positive/negative cutoff criteria were determined according to the maximum SDs obtained from values with the CD19+ B-cell samples.

Statistical analysis. Comparisons between different groups for tumor uptake and survival distribution (mean survival time) were made using a log-rank test. The level of significance was determined at P < 0.05. Differences between various groups for galectin-7 expression were made using a Student’s t test.

Results

Stable transfection of lymphoma cells with antisense galectin-7 RNA. To examine the role of galectin-7 in tumor progression, a cDNA fragment spanning the translational start site of the mouse galectin-7 gene was inserted into the pSRα vector in the antisense direction. The positive plasmid was verified by digestion with restriction enzymes and DNA sequence. The 164T2S11 lymphoma cells were stably transfected with either this antisense construct (S11G7AS) or a construct containing a control sequence (S11Sr). S11 is a mouse lymphoma cell line, which constitutively expresses galectin-7 (Fig. 1). The efficacy of galectin-7 antisense RNA to suppress galectin-7 at both the mRNA and protein levels was then examined by RT-PCR and Western blot in several independently derived clones. We found that galectin-7 expression was almost completely inhibited at both the mRNA and the protein levels in clones C, D, and F compared with control clones transfected with the Srα vectors without the inserted genomic DNA for assessing vector insertion. Galectin-7 expression was monitored by Western blot analysis.

Figure 3. Decreased dissemination of lymphoma expressing galectin-7 antisense. A, survival analysis of 6- to 8-week-old syngeneic C57BL/6 mice injected i.v. via the tail vein with (10^6) galectin-7 antisense transfectants (●, n = 10) or controls (○; n = 12). When clinical signs of lymphoma became evident (dyspnea, running, and splenomegaly), the animals were killed and spleen, kidneys, and liver were harvested and fixed in 10% formalin for histologic examination or processed for RT-PCR or Western blot analysis. The results represent the pool of two independent experiments carried out with two distinct clones. B, effect of the inhibition of galectin-7 on the infiltration of aggressive lymphoma cells in peripheral organs. Histopathology of kidney showing the infiltration of control (S11Sr, right) or galectin-7 antisense (left) lymphoma cells found in the kidney. Magnification, ×400. Infiltration of lymphoma cells transfected with the antisense vector for galectin-7 was milder in the kidney compared with the control, which shows severe infiltration in the cortex. Sections were stained with HE.

Figure 4. Expression of galectin-7 in lymphoid tumors collected from mice at necropsy. A, RT-PCR analysis of galectin-7 mRNA expression in lymphoid tumors located in the kidneys of mice infected with controls (S11Sr) or antisense transfectants (S11G7AS). B, similar analysis on tumors located in the liver carried out by Western blot using anti-galectin-7 polyclonal antibody. C, quantitative analyses of galectin-7 expression in lymphoid tumors collected at necropsy done by image densitometry. The histogram represents the means of independent experiments shown in (A). Statistical analysis was carried out using Student’s t test for unpaired samples. Galectin-7 antisense expression significantly inhibited galectin-7 expression in kidney metastasis (P < 0.001).
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Figure 5. Quantitative expression of galectin-7 in human lymphoid malignancies. Galectin-7 expression at the mRNA level measured by quantitative RT-PCR analysis. Specimens are classified according to the morphologic type of lymphoid disease: CLLs (including one case of transformed CLL), B-cell prolymphocytic leukemia (B-PLL), follicular lymphomas (FL), splenic marginal zone lymphomas (SMZL), mantle cell lymphomas (MCL), lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL), Burkitt lymphomas (BL), and B-cell LPD not classified (NCLPD). CD19+ human B cells were used as negative controls. Horizontal line, positive/negative cutoff criteria were determined according to the maximum SDs obtained from values with the CD19+ B-cell samples. Results are the mean values of two independent experiments carried out in triplicate.

Reduced MMP-9 secretion in lymphoma cells expressing lower levels of galectin-7. Previous studies have shown that members of the galectin family can bind to cell surface receptors expressed on normal or transformed lymphocytes, triggering behavioral changes and/or inducing expression of new genes (7, 21–23). For galectin-7, we have shown, specifically, that it can induce the expression of mmp-9 gene in lymphoma cells (20). Several studies have reported that release of MMP-9 correlated with the tumorigenic phenotype of various tumor cell types, the most compelling evidence of its involvement in tumor invasion being a study showing that MMP-9–specific ribozyme suppresses the metastatic phenotype of tumor cells (24). To determine whether we had achieved a functional inhibition of galectin-7 in our S11 lymphoma cells, we compared the level of mmp-9 gene expression in S11G7AS clones and control clones. Our results showed that mmp-9 gene expression was lower in lymphoma cells containing the antisense galectin-7 cDNA compared with control cells (Fig. 2), consistent with the idea that galectin-7 controls the expression of mmp-9 in lymphoma cells.

Down-regulation of galectin-7 expression results in reduced tumorigenicity of lymphoma cells. To determine whether reduced galectin-7 expression by lymphoma cells leads to impaired lymphoma dissemination and invasion in vivo, antisense-transfected or control-transfected S11 lymphoma cell clones were injected i.v. into syngeneic immunocompetent C57BL/6 mice. Our results showed that mice that expressed the galectin-7–specific antisense in S11 lymphoma cells showed a significantly delayed dissemination and growth of lymphoid tumors compared with mice whose lymphoma cells had been transfected with the control vector (Fig. 3A). Thus, the mean survival time of mice injected with the galectin-7 antisense was significantly longer (32 ± 19.96 versus 14 ± 0.53 days) than that of mice injected with control transfectants (P < 0.001). To investigate in more details the inhibitory effects of galectin-7 on metastasis of S11 lymphoma cells, analysis of galectin-7 expression in tumors collected at necropsy was carried out. We found that galectin-7 expression was substantially reduced in tumors bearing antisense cDNA relative to the controls as assessed by RT-PCR and Western blot, indicating that the levels of galectin-7 remained suppressed in S11G7AS cells in vivo (Fig. 4).

Lymphoma invasion reduced in peripheral organs by down-regulation of galectin-7. Because galectin-7 has been shown to induce mmp-9 gene expression and has previously been shown to promote lymphoma cell infiltration in peripheral organs, we compared the level of tumor cell infiltration in peripheral organs of mice injected with the S11G7AS and S11 cells transfected with the control vector by histochemical staining. As shown in Fig. 3B, we found a significant decrease in the overall infiltration of tumor cells in the kidneys of mice injected with cells containing the antisense cDNA compared with the controls. Similar results were obtained with the liver (data not shown). These results indicate that the tumor-expressed antisense cDNA for galectin-7 has an inhibitory effect on infiltration of tumor cells in target tissues and are therefore consistent with our previous data showing that galectin-7 promotes MMP-9 expression and tissue invasion (20).

Quantitative expression of galectin-7 in human lymphoma cells. Galectin-7 is expressed in human malignant thyroid tumors and type IV hypopharyngeal squamous cell carcinoma (13, 25). We have also shown that galectin-7 is expressed in murine aggressive lymphoma cells but not in normal lymphocytes (14). To study the expression of galectin-7 in human lymphoid cells, we measured the level of galectin-7 mRNA expression by quantitative RT-PCR in 50 specimens of different mature B-cell neoplasms. This group of hematologic malignancies represents over 85% of all known lymphoid neoplasms (19). Our results showed that 18 of 50 lymphoid specimens expressed high levels of galectin-7 transcripts. Eleven of 31 CLLs, 2 of 2 follicular lymphomas, 1 of 5 mantle cell lymphomas and B-cell LPD not classified, and 1 of 2 B-cell prolymphocytic leukemia, Burkitt lymphoma, and splenic marginal zone lymphoma specimens were positive. In contrast, no significant levels of galectin-7 were found in purified human CD19+ B cells isolated from peripheral blood (Fig. 5).

Discussion

In the present work, experimental evidence is provided to show that galectin-7 functions as an important molecule in the dissemination of lymphoma cells in vivo. More specifically, our results showed that stable transfection of lymphoma cells with a
plasmid encoding antisense galectin-7 cDNA markedly inhibited the dissemination and invasion of lymphoma cells to peripheral organs, thereby increasing the survival of mice compared with controls. Additionally, we showed that inhibition of galectin-7 in aggressive lymphoma cells correlated with a decreased invasion of tumor cells in target organs and a reduced expression of mmp-9, a gene associated with a poor prognosis in non–Hodgkin’s lymphoma (26, 27). Finally, we report for the first time high galectin-7 expression levels in a significant proportion of mature B-cell lymphoid neoplasms but not in normal B lymphocytes.

Many galectins have been reported to play an important role in cancer progression (10). At first glance, because galectin-7 functions as a regulator of differentiation and apoptosis in several cell types (16, 28–30), one would expect that galectin-7 should favor the elimination of tumor cells during cancer progression. However, in addition to aggressive lymphoma cells, high levels of galectin-7 expression have been reported in chemically induced rat mammary tumors (12), in human malignant thyroid tissues (13), and in type IV hypopharyngeal squamous cell carcinoma (25). This apparent discrepancy can be explained by the fact that, depending on the cell types, galectin-7 could be preferentially found in the cytoplasm, in the nucleus, or in the extracellular space, thereby having distinct functions according to its cellular localization (29). Alternatively, galectin-7 could modulate distinct biological processes according to specific interactions with a variety of intracellular and extracellular proteins that differ between cell types. Clearly, future investigations should address this issue. In the present case, its inhibition via an antisense strategy was sufficient to severely inhibit the dissemination of metastatic lymphoma cells to peripheral tissues.

Although we were able to achieve a significant inhibition of reduction of lymphoma development in mice, a significant number of mice still developed lymphomas when injected with lymphoma cells expressing the antisense vector specific for galectin-7. Several possibilities can explain this observation. First, it is conceivable that incomplete inhibition of galectin-7 was at least in part responsible for the development of some of these lymphomas. Although we have not detected expression of galectin-7 in lymphoid tumors collected from mice at necropsy, we detected some expression of galectin-7 by RT-PCR in some lymphoid tumors collected at later times. Alternatively, it is probable that other genes can also positively contribute to the aggressive behavior of lymphoma cells. A case in point is MMP-9, which has been associated with a poor prognosis of non–Hodgkin’s lymphoma (26, 27). Whether MMP-9 is essential for the protumorigenic activity of galectin-7 remains, however, to be established. Given the fact that galectin-7 is secreted by lymphoma cells and can bind several receptors expressed on the surface of stromal cells and given the fact that the tumor microenvironment plays a significant role in tumor progression (31), it is also possible that secretion of galectin-7 by aggressive lymphoma cells stimulates peritumoral cells to secrete either mmp gene or other prometastatic genes. Alternatively, galectin-7 could induce apoptosis of infiltrating T cells, a scenario similar to that observed with extracellular galectin-3, which may act as a proapoptotic factor (32). These possibilities are currently under investigation.

This study reports galectin-7 expression for the first time across a broad spectrum of B-cell lymphoid malignancies. Analysis of a larger number of samples will be necessary to establish whether expression levels of galectin-7 correlate with the most aggressive forms of the diseases or with tumor recurrence rates as recently shown for hypopharyngeal squamous cell carcinoma (25). Nevertheless, we were able to confirm that galectin-7, a gene previously considered as a keratinocyte marker and whose expression is restricted to stratified epithelia, is commonly expressed in several forms of human and mouse lymphoid disorders but not in normal lymphocytes. Questions can be asked about the mechanisms responsible for increased galectin-7 levels in lymphoid malignancies. Interestingly, four of five patients have the highest levels of galectin-7 mRNA (the two cases of CLL and the two patients with follicular lymphoma), which is at first somewhat at odds with a previous study showing that galectin-7 is under the control of p53 (33). Whether the other p53 allele is functional or is mutated remains to be tested. In fact, the association of galectin-7 with p53 should normally aid the host against tumor development. This is so neither in our case nor for head and neck squamous cell carcinomas (25) and possibly also in mammary carcinomas (12). Previous results showing that hypomethylating agents induce the expression of galectin-7 in lymphoma cells suggest that epigenetic mechanisms may play an important role in this process and/or that cell-specific transcriptional mechanisms may be involved. This issue is currently under investigation.

In summary, we now document for the first time that galectin-7 is expressed in human lymphoid malignancies and propose that it is a critical tumor-modulating gene that controls the dissemination of lymphoma cells via MMP-9. Based on the importance of these molecules and the biochemical pathways they regulate, galectin-7 may significantly affect lymphoma progression in the clinical setting.

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