Exp Oncol 2009
31, 2, 74–79

Experimental ONCOLOGY

EXPRESSION OF GALECTIN-1 IN MALIGNANT TUMORS

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Galectin-1 is a 14 kDa lectin expressed ubiquitously in mammalian organism. Since its discovery, the lectin was shown to participate in many cellular processes. Involvement in some of them like induction of apoptosis of activated T cells, mediation of cell adhesion and participation in angiogenesis suggest that galectin-1 could be utilized by malignant tumors. Indeed expression of galectin-1 is upregulated in tumors of different origin. Many examples point to its important role in a process of cancer metastasis. This review summarizes the data available to date on galectin-1 expression in human malignancies.
Key Words: **galectin-1, cancer, cancer prognosis, cancer treatment.**

Galectin-1 is one of the most important lectins to date participating in the malignant tumor development. With more and more data available on its expression in tumors it is already clear that this lectin is an important target for cancer diagnostics and treatment.

Described in the 1980s, galectin-1 was more extensively studied in 1990s. Its first involvement in cancer was associated with cell adhesion [1]. Later on the lectin was shown to induce apoptosis of activated T-cells [2], and experiments have confirmed [3] that cancer cells express galectin-1 also to protect themselves from immune response. Latest finding is a participation of galectin-1 in tumor angiogenesis as an angiogenic factor [4]. Galectin-1 participation in various cellular processes is well reviewed [5–7].

A purpose of this review was to summarize the data obtained to date on galectin-1 expression in human cancers and possibility of its use in diagnostics and prognosis of the disease outcome. The data is summarized according to tumor origin. The tumor sites are listed according to the frequency of tumor occurrence published by American Cancer Society, the Centers for Disease Control and Prevention, the National Cancer Institute, and the North American Association of Central Cancer Registries [8].

Prostate. Studies of two LNCaP prostate carcinoma cell line variants as a model of androgen dependent and independent prostate cancer showed that galectin-1 expression is increased in androgen independent LNCaP cell line variant [9]. Androgen dependent LNCaP cell line variant appeared to be susceptible to galectin-1 induced apoptosis [10]. Presence of core 2N-acetylglucose-aminyl transferase, the enzyme which catalyzes addition of polylactose-amine sequences crucial for galectin-1 binding to O-glycans on cell surface receptors was crucial for apoptosis of androgen dependent LNCaP cell line variant induced by galectin-1 [11]. Increased expression of galectin-1 was observed in stroma of primary prostate carcinoma samples in comparison to stroma of normal prostate, and increased galectin-1 expression positively correlated with a poor prognosis of disease outcome [12].

Endothelial cells of capillaries infiltrating to tumor stroma have strongly increased expression of galectin-1 in comparison to endothelial cells of capillaries in adjacent normal stroma [13]. Hypothesis of the authors that carcinoma cells induce galectin-1 expression in endothelial cells was confirmed by incubation of endothelial cells with conditioned media from PC-3 or DU145 prostate carcinoma cells, which significantly increased galectin-1 expression in endothelial cells. Adhesion of PC-3 prostate carcinoma cells to endothelial cells expressing galectin-1 was increased in comparison to endothelial cells not expressing galectin-1 [13].

Lung. Examination of 159 cases of lung cancer patient specimens for their capacity to bind galectin-1 demonstrated that patients showing expression of galectin-1 binding sites revealed a better prognosis than those lacking binding sites or showing a weak reactivity [14].

Galectin-1 protein expression was increased in BEAS 2B (human normal lung epithelial cells) in comparison to A549 (human malignant lung epithelial cells) [15].

In studies of atypical adenomatous hyperplasia (AAP) of lung (suggested to develop to peripheral localized lung carcinomas) alveolar lining cells from AAP were found to express higher level of galectin-1 and galectin-1 binding sites. The cells formed spatial clusters. AAP in general was characterized by increased vascularisation in comparison to normal tissues [16].

Galectin-1 expressing lung tumors where shown to have poorer prognosis than non expressing ones by Szoke T. *et al.* [17, 18].

Received: April 24, 2009.
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Abbreviations used: AAP – atypical adenomatous hyperplasia; C2GnT-I – 2 beta-1,6-N-acetylglucosaminyltransferase; CD – cluster of differentiation; CRD – carbohydrate recognition domain; DLBCL – diffuse large B cell lymphoma; FTS – farnesylthiosalicylic acid; GTP – guanosine tri-phosphate; HER2/neu – Human Epidermal growth factor Receptor 2/neuroglioblastoma; HL – Hodgkin lymphoma; HMEC – human mammary epithelial cell; HNSCC – head and neck squamous cell carcinoma; H-Ras – Harvey sarcoma Ras; ICC – intrahepatic cholangiocarcinoma; L-PHA – leuko-phytohemagglutinin; MAPK – mitogen activated protein kinase; MMP – matrix metalloproteinase; mTOR – mammalian target of rapamycin; OSCC – oral squamous cell carcinoma; PLC – phospholipase C; Ras – rat sarcoma; TGF – tumor growth factor; VEGF – vascular endothelial growth factor.

Reduced proliferation accompanied by downregulation of galectin-1 was observed after treatment of a lung carcinoma cell line A549 with extract of fungus *Antrodia camphorata* [19]. Galectin-1 was also identified among secreted proteins from A549 lung carcinoma cells [20].

Invasiveness of CL1-5 lung adenocarcinoma cell line was shown to correlate positively with a level of galectin-1 expression by the cell line [21].

Breast. Galectin-1 is expressed by MDA-MB-435 human breast carcinoma cells and is accumulated in the contact site between MDA-MB-435 and human umbilical endothelial cells suggesting the role for galectin-1 in adhesion of the breast carcinoma cells [22].

Different breast cancer cell lines express galectin-1 mRNA as it was shown by Lahm *et al.* [23]. The overexpresion of proto-oncogene receptor HER2/neu (Human Epidermal growth factor Receptor 2/ neuroglioblastoma) in immortalized human mammary luminal epithelial cells upregulated expression of 35 genes including galectin-1 gene [24].

Farnesylthiosalicylic acid (FTS), which blocks the binding of GTP-H-Ras(12V) to its membrane acceptor protein, galectin 1, blocks the functionality of Ras and the activity of mTOR [25]. FTS also effectively inhibits the proliferation of MCF-7 breast cancer cells in culture [25]. Since this agent blocks MAPK as well as mTOR, it may be useful for the prevention of adaptive hypersensitivity and prolongation of the effects of hormonal therapy in breast cancer.

Galectin-1 expression was detected in both drug-sensitive MCF-7 and drug-resistant MCF-7/AdrR cells [26]. Galectin-1 was present in the cytosol, on the surface of the cells and in the culture media.

Galectin-1 was shown to be a substrate of matrix metalloproteinase (MMP)-14 expressed by breast cancer cells [27].

In metastatic mammary adenocarcinoma LM3 and MCF-7 cells galectin-1 expression is increased in response to treatment with TGF-beta (tumor growth factor beta) [28]. Galectin-1 was identified as a metastasis associated protein in the studies of two clones of human breast carcinoma cell line MDA-MB-435 with different metastatic potential [29]. Correlation between increased expression of galectin-1 in cancer associated stromal cells and tumor invasiveness was also shown [30]. Proteomic profiling of seven breast cancer cell lines (MDA-MB-231 (metastatic), HCC1428, AU565, MDA-MB-468, SK-BR-3, MCF7 and BT-474) in comparison to normal human mammary epithelial cell (HMEC) line demonstrated that galectin-1 is upregulated in the metastatic cell line MDA-MB-231 in comparison to the rest of the cancer cell lines studied [31].

Colon. Galectin-1 expression was much higher it the stromal cells of colorectal carcinomas than adenomas and normal tissue as was it shown by Sanjuan X. *et al.* [32].

Expression of galectin-1 and its binding sites was higher in mild dysplasias, severe dysplasias and invasive carcinomas of the colon than in normal cases [33]. From four cell lines (HCT-15, LoVo, DLD-1 and CoLo201), only CoLo201 expressed galectin-1 mRNA and protein. From the cell lines only DLD-1 was not able to bind galectin-1. Galectin-1 added to the media had no effect on growth of the cell lines. The level of galectin-1 expression was related inversely to the growth rate of HCT-15, LoVo, DLD-1 and CoLo201 cells xenografted *in vivo* into nude mice - the higher was the galectin-1 expression level, the lower was growth rate of the cells. The influence (inhibition) of galalectin-1 on migration of HCT-15, LoVo, and CoLo201 was also shown [33].

Patients with galectin-1 positive colon tumors on Dukes A (invasion into but not through the bowel wall) and Dukes B (invasion through the bowel wall but not involving lymph nodes) stages had shorter survival periods than those with galectin-1 negative colon tumors on the same stages [34].

Important role for galectin-1 in adhesion of colon cancer cell line with metastatic phenotype CoLo 201 was demonstrated [35]. The regulation of adhesion was dependent on carbohydrate binding ability of galectin-1. MAPK and PLC inhibitors decreased the adhesion. Intracellular galectin-1 overexpression induced apoptotic cell death in CoLo 201 cells, while exogenous galectin-1 was not able to induce apoptosis in these cells [35].

Galectin-1 expression is upregulated in KM12 human colon carcinoma cell line upon sodium butyrate treatment [36]. The treatment induces acquisition of differentiated phenotype by the cell line. There is an interesting observation that although HCT-116 and HT-29 colon cancer cell lines express galectin-1 mRNA, only HCT-116 cells express the protein [26].

Urinary tract, kidney. Bladder transitional cell carcinomas were examined for the level of expression of galectin-1 mRNA [37]. Higher grade tumors expressed significantly higher levels of galectin-1 mRNA than low grade tumors or the cells of normal bladder. Western blot and imunohystochemical analysis showed similar results on the protein level.

Galectin-1 expression is upregulated in bladder cancer tissue in comparison to normal bladder tissue as it was shown by Sheng K.H. *et al.* [38].

Galectin-1 mRNA is upregulated in cytoplasm of parenhimal cells of urothelial tumors, and upregulation correlates with tumor grading [39].

Lymphoid tissue. Treatment of diffuse large B cell lymphoma (DLBCL) cell line HBL-2 and Burkitt's lymphoma cell line HBL-8 with neuraminidases, which remove sialic acid from the cell surface, enhances their adhesion to galectin-1 [40]. The sialation could have a clinical outcome since diffuse large B cell lymphoma patients with sialylated type of leuko-phytohemagglutinin (L-PHA) reactive oligosaccharides had a poor prognosis.

Upregulation of galectin-1 as well as galectin-1-binding carbohydrates expression in cutaneous T cell lymphomas (CTCL) in comparison to pseudolymphoma and atopic dermatitis was demonstrated [41]. Chemotherapy with pegylated liposomal doxorubicine decreased the expression of galectin-1 and galectin-1-binding carbohydrates in CTCL.

$CD7^-$ cells of the early stages of cutaneous T cell lymphoma (Sezary syndrome) were resistant to galectin-1 induced cell death, what possibly led to their accumulation at the late stages of the disease [42]. Although SeAx/i $CD7^+$ cell line was susceptible to galectin-1 induced apoptosis, $CD7^+$ HH cell line was not susceptible to galectin-1induced apopotosis suggesting that altered glycosilation of CD7 was responsible for this [42]. It was shown that the basis for resistance to galectin-1 induced cell death in $CD7^+$ HH cells from mucosis fungoides is in core 2 beta-1,6-N-acetylglucosaminyltransferase (C2GnT-I) deficiency [43]. C2GnT-I is the enzyme, which creates core 2 O-glycan ligands for galectin-1.

Galectin-1 was expressed in Hodgkin lymphoma (HL) cell lines L540, L1236, HDLM2, L428. 26 of 42 cases of classic HL were positive for galectin-1, whereas nodular lymphocyte predominant HL was negative for galectin-1 [44]. High expression of galectin-1 was associated with male gender, older patients, reduced $CD8^+$ T cell infiltration at the tumor site, and an impaired latent membrane protein 1 and 2-specific $CD8^+$ T-cell responses. Proliferation and interferon-gamma expression by Epstein — Barr virus-specific T cells was inhibited by exposure to recombinant galectin-1 *in vitro*.

Neoplastic Reed–Sternberg (RS) cells of classical Hodgkin lymphomas (cHL) overexpressed galectin-1. Galectin-1 was directly involved in maintenance of immunosuppressive microenvironment in cHL [3].

Galectin-1 is selectively expressed by malignant RS cells in > 90% of primary cHLs in contrast to diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, and nodular lymphocyte-predominant Hodgkin lymphoma which do not express the lectin [45]. The anaplastic large cell lymphomas (ALCL) also express galectin-1.

Skin. Galectin-1 mediates A375 and A2058 melanoma cell lines adhesion to laminin in carbohydrate dependent fashion [46].

Blocking of galectin-1 expression *in vivo* stimulates antitumor immunity and promotes tumor rejection in a case of melanoma in mice [47].

Pancreas. Significantly higher level of galectin-1 was detected in pancreatic cancer tissue stromal fibroblasts and extracellular matrix, than in normal pancreatic tissue [48]. Galectin-1 mRNA and protein levels were significantly higher in poorly differentiated tumors than in that of well/moderately differentiated. Pancreatic cancer metastases showed no galectin-1 expression. Galectin-1 protein was upregulated in pancreatic ductal adenocarcinoma in comparison to normal pancreatic tissue [49].

Upper digestive tract. Galectin-1 was upregulated in tongue carcinoma tissues compared to normal mucosa [50].

The lectin was overexpressed in the tumor-associated stroma of the oral squamous cell carcinomas (OSCC) as well as the invasion front during early oral carcinogenesis [51]. During the metastasis significant galectin-1 expression was detected only at the tumor invasion front. It is suggested that galectin-1 upregulation at the tumor invasion site might be a predictor of early metastasis in oral carcinogenesis.

Galectin-1 is upregulated in cancer-associated endothelial cells in the specimens of OSCC in comparison to adjacent nontumor mucosa [52]. It was also demonstrated that galectin-1 increased the proliferation and adhesion of endothelial cells (EC), and enhanced EC cell migration in combination with VEGF.

Invasivness of OSCC cell lines positively correlates with galectin-1 expression [21]. Decrease of galectin-1 expression in most invasive HSC-3 cell line caused by siRNA to galectin-1, decreased invasiveness of the cell line. In contrary, overexpression of galectin-1 in poorly invasive OEC-M1 cell line increased invasiveness. It was also shown that in OSCC tissue galectin-1 was upregulated in metastatic lesions in lymph nodes in comparison to primary tumor sites.

Epithelial tissues in head and neck squamous cell carcinomas (HNSCC) exhibited lower amounts of galectin-1 and their respective binding sites than their corresponding normal counterparts [53].

Galectin-1 expression is upregulated and secretion to the media is induced by hypoxia in FaDu cells (cell line of a squamous cell carcinoma of the hypopharynx) [54]. Staining of tumor tissues from 101 HNSCC patients showed correlation of expression of galectin-1 and carbonic anhydrase IX (a hypoxia marker). Galectin-1 and CD3 (T cell marker) staining could be used in prognostic purposes. Three groups could be distinguished — favourable (negative to weak galectin-1 staining and strong CD3 staining), intermediate (strong staining for both markers or negative to weak staining of both markers) and unfavourable (strong galectin-1 and negative to weak CD3 staining).

Serum galectin-1 levels are higher in patients with HNSCC and successful treatment reduces galectin-1 content in serum as it was shown by Saussez S. *et al.* [55].

Thyroid gland. Most aggressive and undifferentiated anaplastic thyroid carcinomas consistently exhibited a marked increase of galectin-1 expression [56].

Thyroid malignancies of epithelial origin (i. e., papillary and follicular carcinomas) and metastatic lymph nodes from a papillary carcinoma expressed high levels of galectin-1 [57]. Medullary thyroid carcinomas had weaker and variable expression of galectin-1. Benign thyroid adenomas and adjacent normal thyroid tissue expressed no galectin-1.

Concentration of galectin-1 was increased in the sera of patients with benign thyroid lesions in comparison to healthy individuals [58].

Stomach. Examination of transcription profiling of metastatic gastric cancer TMC-1 cells and the non-invasive gastric cancer SC-M1 cell showed higher galectin-1 expression in TMC-1 cells suggesting galectin-1 as a metastasis marker in gastric cancer [59].

Brain, nervous system. High galectin-1 mRNA levels in glioma tissues and glioma cell lines was demonstrated [60]. High galectin-1 protein content in glioma tissues was confirmed by immunohisochemistry.

Galectin-1 expression is higher in astrocytomas, anaplastic astrocytomas, glioblastomas in comparison to pilocytic astrocytomas [61]. All glioblastoma cell lines examined contained galectin-1.

Expression of galectin-1 was shown in all studied human glioma types [62]. The level of galectin-1 expression correlated with the grade only in the group of astrocytic tumors. Patients with high-grade astrocytic tumors that had high level of galectin-1 expression, had shorter survival periods than those with low level of galectin-1 expression. In human glioblastoma xenografts, galectin-1 was preferentially expressed in the more invasive parts of these xenografts. The authors also showed that migration of U373 astrocytes was stimulated by galectin-1.

Immunohistochemical analysis of galectin-1 expression of human U87 and U373 glioblastoma xenografts from the brains of nude mice showed a higher level of galectin-1 expression in invasive areas of the xenografts in comparison to the non-invasive areas [63]. Galectin-1 added to the culture media increased cell motility levels of human U87 glioblastoma cells.

Temozolomide (the standard treatment for glioma patients), increases galectin-1 expression in human Hs683 glioblastoma cell line, and the reduction of galectin-1 expression in these cells by siRNA increases the anti-tumor effects of temozolomide as well as the other chemotherapeutic agents [64].

Galectin-1 expression in the human glioblastoma multiforme cell lines positively correlated with migratory abilities and invasiveness [65]. Analysis of human glioma samples revealed that increased galectin-1 expression was associated with a higher tumor grade.

Ovary. Examination of galectin-1 expression in 30 human epithelial ovary carcinoma samples by Western and Northern blotting and by immunohistochemistry showed that 95% of ovary carcinoma samples had higher galectin-1 mRNA level and 57% higher protein level in cancer epithelial cells in comparison to normal ovary [66]. Higher level of galectin-1 was detected by immunohistochemistry in stroma of carcinomas than in stroma of normal ovary. Galectin-1 protein expression was detected in AZ364, SK-OV-3, and AZ224 but not in OVCAR-3, AZ419, and AZ382 human ovary carcinoma cell lines. Conditioned media from AZ364, AZ224, OVCAR-3, AZ382 induced galectin-1 expression in cultured 84BR fibroblasts. Positive influence of galectin-1 on above mentioned cell lines adhesion to laminin and fibronectin was also shown.

Liver. Galectin-1 expression was shown by immunohystochemistry in intrahepatic cholangiocarcinoma (ICC) while no galectin-1 expression was seen in normal bile ducts [67]. ICC cells with higher galectin-1 expression level had higher proliferation rate. Galectin-1 was also strongly expressed in the cancerous stroma of ICC. Cholangiocarcinoma cell line, CCKS1 expressed galectin-1 in the cytoplasm and secreted to the medium.

Galectin-1 mRNA was upregulated in primary hepatocellular carcinomas in comparison to non tumor liver tissues [68].

Myeloid tissue. Galectin-1 is expressed in bone marrow samples of multiple myeloma patients. The lectin promotes survival of $CD45RA^-$ primary myeloma cells and myeloma cell lines, while reduces the viable cell number in $CD45RA^+$ B cell lines [69].

Uterine, cervix. Galectin-1 expression is increased in endometrial cancer cells in comparison to normal adjacent endometrium [70].

Galectin-1 expression in stromal cells adjacent to neoplastic endothelia in cervical neoplasias increases with elevation of histopathologic grade of cervical tissues [71]. Number of samples with strong staining for galectin-1 increased from low-grade squamous intraepithelial lesions to high-grade squamous intraepithelial lesions and to invasive squamous cell carcinomas.

Galectin-1 binding inhibitors. (E)-methyl 2-phenyl-4-(b-D-galactopyranosyl)-but-2-enoate 15 was shown to be a selective inhibitor of galectin-1 carbohydrate recognition domain (CRD) with inhibitory potency of 313 μM [72]. Divalent carbamate 19, one of the 1,4-substituted 1,2,3-triazoles with a K_d value as low as 3.2 μM for galectin-1, was described by Tejler *et al.* [73]. There are also other molecules with inhibitory potency for galectin-1 CRD described by different groups (not cited due to space restrictions).

Although with most of the binding partners galectin-1 interacts through its CRD, it is worth mentioning that the lectin also interacts with oncogenic form of H-Ras (H-Ras(12V)) in complex with GTP, stabilising anchorage of the complex to the membrane and promoting oncogenic transformation by activated H-Ras(12V). This interaction is blocked by farnesylthiosalicylic acid [74].

CONCLUDING REMARKS

In most of the cases described, galectin-1 is upregulated in tumors in comparison to normal tissue. Moreover, the presence of the lectin is associated with metastases and poor prognosis of disease outcome. Taking all above mentioned into account, the use of galectin-1 detection for diagnostics of cancer should be promoted and use of galectin-1 inhibitors as well as siRNA in combination with other antitumor agents should be considered. It is necessary to note that the expression of galectin-1 on mRNA level is not always accompanied by protein expression [26].

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