Human Immunology 76 (2015) 770–774

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

Review

Role of galectin-3 in the pathogenesis of bladder transitional cell carcinoma

Masoud Zeinali [a], Armin Adelinik [b], Shaghayegh Papian [c], Hossein Khorramdelazad [d], Mehdi Abedinzadeh [e,*]

[a] Social Determinants of Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
[b] Department of Reproductive Genetics and Biotechnology, Avicenna Research Institute, Tehran, Iran
[c] Department of Medical Bacteriology, Tarbiat Modares University, Tehran, Iran
[d] Molecular Medicine Research Center, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[e] Department of Urology, Shahid Rahnemoon Hospital, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

ARTICLE INFO

Article history:
Received 17 November 2014
Revised 19 August 2015
Accepted 27 September 2015
Available online 30 September 2015

Keywords:
Bladder cancer
TCC
Galectin-3
Tumor

ABSTRACT

Galectins constitute an evolutionary conserved family that binds to β-galactosides. There is growing evidence that galectins are implicated in essential biological processes such as cellular communication, inflammation, differentiation and apoptosis. Galectin-3 is one of the best-known galectins, which is found in vertebrates. Galectin-3 has been shown to be expressed in some cell lines and plays important roles in several physiological and pathological processes, including cell adhesion, cell activation and chemoattraction, cell cycle, apoptosis, cell growth, and differentiation. Moreover, this galectin is of interest due to its involvement in regulation of cancer. Changes in galectin-3 expression are commonly seen in cancerous and pre-cancerous conditions and galectin-3 may be involved in the regulation of cancer cell activities that contribute to tumourigenesis, cancer progression and metastasis. Finally, galectin-3 seems to be involved in cell events in tumor microenvironment, and therefore it could be considered as a target in transitional cell carcinoma therapies. This review aims to describe recent progress in understanding the role of galectin-3 in cancer biology, with emphasis on bladder tumor progression and metastasis.

Contents

1. Introduction

Bladder cancer is the most frequent malignancy of the urinary tract, causing approximately 150,000 deaths annually [1]. It is the fourth most common cancer in men and is clinically characterized by high recurrence rates and poor prognosis once tumors invade the muscular layer [2]. None of the serum or urinary diagnostic tumor biomarkers evaluated to date has provided sufficient sensitivity and specificity for the detection and follow-up of patients with bladder cancer in clinical routine practice. Therefore, development of prognostic biomarkers is needed; the use of such markers should ultimately distinguish indolent cancers from those

* Corresponding author.
E-mail address: abedinoro@yahoo.com (M. Abedinzadeh).

http://dx.doi.org/10.1016/j.humimm.2015.09.036
0198-8859/

that are potentially lethal so that therapeutic procedures can be tailored to each individual patient [3].

Galectins are a family of carbohydrate-binding proteins characterized by a high affinity for β-galactosides and a conserved amino-acid sequence [4]. There are 14 known galectins from mammals that are classified based on their structural properties [5–7]. Galectins contribute to tumourigenesis, proliferation, angiogenesis, and metastasis in cancer [8]. The expression pattern of galectins, especially galectin-3, is altered in many cancer types. When localized in the plasma membrane and extracellular matrix, galectin-3 mediates cell–cell and cell–matrix interaction. Its nuclear expression is responsible for the regulation of gene transcription and pre-mRNA splicing. Galectin-3 is found in cytoplasm and nucleus where it regulates apoptosis and proliferation [4,8,9]. A differential expression of galectin-3 in bladder cancer has been suggested [10]; however, its role in the progression of bladder cancer has not been comprehensively evaluated. On the other hand, it has been shown that galectin-1 and -3 are upregulated in bladder transitional cell carcinoma [11]. Both of these galectins are involved in the regulation of cellular growth, differentiation, and malignant tumor progression [12].

2. Structure and function of galectin-3

Galectins are a family of animal lectins defined by their affinity toward b-galactosides and the presence of at least one evolutionary conserved carbohydrate-binding domain [13]. They have been found in all metazoans examined, from sponges and fungi to invertebrates and vertebrates. To date, 15 galectins have been recognized in mammals; they are broadly distributed among different types of cells and tissues. Human galectin-3 is a 35 kDa protein coded by the single gene LGALS3 located on chromosome 14. LGALS3 is composed of six exons and five introns spanning a total of ~17 kb.

Exon IVeVI encodes the C-terminal domain containing the carbohydrate recognition domain (CRD). Exon III and 18 bp of exon II encode a long and flexible N-terminal domain that contains sites for serine phosphorylation and other determinants that are important for the non-classical secretion of the protein. Galectin-3 is classified as a chimera-type galectin because of the presence of an N-terminal domain adjacent to the CRD. Like most members of the galectin family, it binds glycoconjugates containing N-acetyllactosamine, but its affinity toward ligands is modulated by the presence of additional saccharides near the galactose remains. Differential recognition of cell surface glycans by different galectins correlates well with their distinct biological and signaling activities [13,14]. Galectins are unique among animal lectins. They can be found in the nucleus, cytoplasm, cell surface, extracellular matrix, and biological fluids. Even though galectin-3 exists as a monomer in solution, it can self-associate through intermolecular interactions involving the N-terminal domain when bound to a multivalent ligand and, therefore, can intervene crosslinking of glycoproteins. The effects of galectin-3 are complex; intracellular forms typically protect cells against apoptosis through carbohydrate-independent mechanisms. Extracellularly, the lectin mediates cell–cell and cell–matrix interactions and promotes apoptosis by binding to lactosamine-containing cell surface glycoconjugates via the CRD.

A number of recent studies have discovered that galectin-3, by binding and cross-linking glycans on cell surface receptors, modulates signal transduction. For example, galectin-3 increase corneal epithelial cell migration by cross-linking complex N-glycans on the a3b1 integrin and inducing lamellipodia formation by activating the a3b1 integrin-Rac1 signaling pathway [15]. It modulates VEGF- and bFGF-mediated angiogenesis by binding via the CRD to N-glycans on integrin avb3 [16]. It also modulates the function of EGF and TGFb receptors. Galectin-3 also forms a cell surface lattice, which is important to barrier function of the ocular surface, through interactions with mucin O-glycans at the apical membrane of corneal epithelial cells [17]. In addition to the cornea, galectin-3 has been detected in the conjunctiva, trabecular meshwork, retina, and in the lens, where it plays a role in cell differentiation and adhesion of fiber cells by interaction with MP20, a member of the tetraspanin superfamily of integral membrane proteins. Studies on non-ocular tissues have shown that galectin-3 is expressed in inflammatory cells such as monocytes, macrophages, dendritic cells, neutrophils and mast cells.

3. Galectin-3 in immune response and cancer biology

Information on functional properties of galectin-3 strongly suggests its importance in the regulation of the immune response and inflammation [18,19]. Galectin-3 is a dominant pro-inflammatory indicator [20]. Special cells produce and emit a large amount of galectin-3 in response to various provocative stimuli. While secreted or externalized, galectin-3 could affect inflammatory cells by means of an autocrine or paracrine mechanism [21]; it triggers/promotes respiratory burst in neutrophils and monocytes and induces mediator release by mast cells [22,23]. It also promotes adhesion of human neutrophils to laminin and endothelial cells and acts as a chemoattractant for monocytes and macrophages [24,25].

Galectin-3 secreted by tumor cells may effectively or preferentially activate antigen-experienced or tumor-reactive T cells to deliver cytokines and prompt apoptosis at a high level of concentration, thus inducing immune tolerance at tumor sites. Similar to other members of galectin protein family, galectin-3 is highly expressed in numerous tumor cell types [26–28]. In addition to its regulatory role in T-cell activation and immune tolerance, galectin-3 may be associated with tumor development as well as the destructive phenotype of tumors [29,30]. Intracellular galectin-3 supports tumor growth, metastasis, and survival [31]. However, some studies revealed that the soluble form of galectin-3 did not influence the development of tumor cells; instead, it balanced the tumor-responsive T-cell function by inducing T-cell activation and apoptosis in vitro [32]. More importantly, soluble galectin-3 hinders T-cell responses and promotes tumor growth in vivo. Given the elevated expression of galectin-3 in tumor cells as well as in the serum of patients suffering from cancer [30,33,34], galectin-3 could accumulate in the local tumor environment, creating the high concentrations required for the above detected effects. The extraordinary concentrations of galectin-3 in the local tumor environments might ultimately drive tumor-reactive T-cell apoptosis and thereby the loss of their antitumor effector roles. In support of this, one study using immunohistochemical staining indicated that the expression of galectin-3 in human melanoma biopsies correlates with T-cell apoptosis [35]. Treatment of rats with galectin-3 inhibitor decreases the progression of human cancer cells in vivo [36–38]. Perhaps galectin-3 prevents antitumor immunity and helps tumor development through two separate mechanisms. Inhibition or knockdown of galectin-3 not only moderates tumor development but also promotes the therapeutic potential of cancer immunotherapy.

There is a large amount of published data on galectin-3 expression in cancer. Altered expression of galectins such as galectin-1 and galectin-3 has been reported in many studies and the role of galectin-3, however, seems to depend on the cancer type. In contrast to gastric cancer, increased expression of galectin-3 is a sign of poor overall survival in colon cancer, brain cancer and acute myeloid leukemia. High expression of galectin-3 in tumor tissue

and serum may be useful as a target for treatment of cancer patients [39]. Since the results have been inconsistent, it is not possible to arrive at a general conclusion about the role of galectin-3 in cancer. These inconsistencies were the consequence of the different experimental approaches that had been used in these studies and the high specificity of each type of cancer, even though all cancers share common distinctiveness such as disturbed adhesiveness and resistance to apoptosis. It is clear that lectin plays multiple roles in cancer pathogenesis, proliferation and metastasis. The intensity of galectin-3 expression and its intracellular distribution has been found to be altered in certain kind of cancers. Fascinatingly, nuclear localization of galectin-3 is mainly related to its anti-tumor effects, whereas its cellular localization correlates with neoplastic progression [40–43]. The progression from primary to metastatic tumors is a multigenic and multistep process involving cell–cell and cell-extracellular matrix (ECM) adhesion, cell invasion and/or movement and angiogenesis. Different galectins seem to play roles in different steps of the processes. Some members interact with integrins to mediate tumor cell adhesion, including adhesion to ECM proteins and homotypic cell adhesion that could result in tumor cell detachment. The overall effect can be the promotion or inhibition of metastasis. Galectin-1 (Gal-1), Gal-3, and Gal-8 can influence tumor cell migration and invasion by engaging integrins or other cell-surface proteins involved in cell migration. In addition, altered expression of galectin-3 has been shown to be associated with tumor metastasis and invasiveness in different types of cancer [44]. Galectin-3 can affect the intrinsic motility of cells by remodeling cytoskeletal elements associated with cell spreading microfilaments by as yet unidentified mechanisms and promote angiogenesis by promoting endothelial cell migration [45] (Fig. 1). It has been found to be overexpressed in glioblastoma, lung, and thyroid carcinomas, where it is involved in tumorgenesis, tumor progression and metastasis [5,46–48]. In gastric cancer, high serum levels of galectin-3 were strongly correlated with diagnosis and metastasis, suggesting its potential diagnostic value in these patients [49]. Other studies recommend caution in interpretation of the results. Galectin-3 has recently been detected in serum and tissue of patients with thyroid carcinoma. The results showed that its serum concentration and tissue expression may help to diagnose thyroid cancers [50]. Recent reviews provide more detailed information on galectin-3 in cancer [4,29,30,51,52].

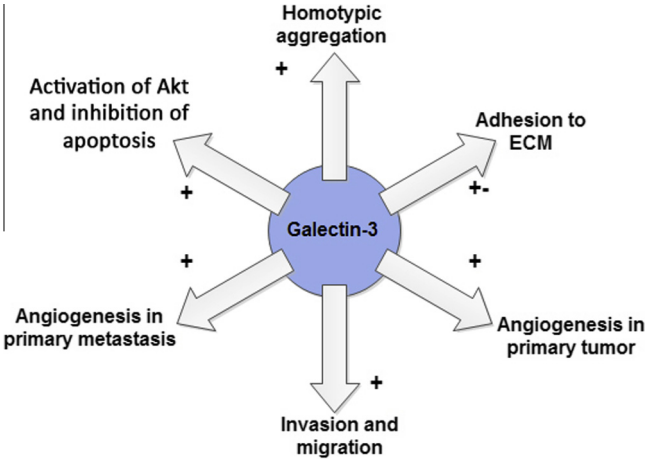

Fig. 1. Galectin-3 modulates tumor cell behavior. Galectin-3 aid developing of tumor with promotion of angiogenesis in either primary tumor or metastasis. It also can inhibit apoptosis throughout Akt pathway activation. In the extracellular space, galectin-3 monomers interact with innumerous glycosylated molecules, including receptors, cell–cell adhesion molecules, integrins as well as, ECM molecules. This complex cross-links carbohydrate-containing glycans, promote the formation of organized galectin–glycan clusters called lattices which modulates tumor cells behaviors and functions, such as adhesion, aggregation and migration.

Additionally, several studies has been investigated the role of galectin-3 in vascular biology. Overexpression of galectin-3 increase collagen type I synthesis, resulting in vascular fibrosis [53]. High levels of circulating galectin-3 lead to secretion of interleukin-6 (IL-6) and granulocyte colony-stimulating factor (G-CSF), which promote metastasis, from blood vascular endothelial cells. Therefore, circulating galectin-3 could be a potential target for preventing metastasis in cancer patients [54]. Galectin-3 expression has been also found to result in cervical cancer cell invasion induced by vascular endothelial growth factor C (VEGF-C) [55].

4. Galectin-3 and TCC (transitional cell carcinoma)

Galectins could be potential markers for early tumor recognition, long-term prognosis and a better-founded choice of therapy. Galectin-3 is an intracellular secreted carbohydrate-binding protein and acts as a regulator of the cell cycle, inflammation, immune responses, cell adhesion, and cell signaling events [9,56]. Anti-apoptotic activity is possible cause for the involvement of galectin-3 in carcinogenesis [57]. It has been shown to be the only galectin with anti-apoptotic activity, as proven by knock-out mice with increasing rates of apoptosis. Intracellularly, galectin-3 can associate with Bcl-2 proteins, an antiapoptotic family of proteins, and may enhance Bcl-2 binding to the target cell. Galectin-3 can also be pro-apoptotic and mediate T cell and neutrophil death [57]. Detection of galectin-3 in body fluids has previously been reported in serum with significantly higher levels in patients having breast, gastrointestinal, lung, and ovarian cancer, non-Hodgkin's lymphoma, and melanoma than healthy individuals [58,59]. The expression patterns of galectin-1 and 3 have been researched extensively. For example, patients with bladder tumors showed an elevated serum level of galectin-3 [10]. Pathological patterns of galectin expression have been detected in non-urological malignancies such as breast cancer. Francois et al. [60] found that the involvement of galectin-3 in the development and progression of transitional cell carcinoma of the urinary bladder has been rarely investigated. Although Cindolo et al. observed an increased expression of galectin-3 in bladder cancer specimens when compared with non-malignant urothelium as detected at the mRNA level by northern blot analysis, a correlation between mRNA levels and further tumor characteristics such as stage and grade were not evident. However, galectin-3 was highly expressed in high-grade tumor tissues (G2 and G3) in comparison to low-grade tissues [10]. For bladder cancer, an initial report evaluated the messenger levels of a series of 38 bladder tumors by RT-PCR. An increase was observed in galectin-3 expression in invasive tumors, which was correlated with poor survival in patients with advanced cancer. In addition, urinary samples had diagnostic values (protein levels of galectin-3) in bladder cancer patients. Cindolo et al. reported that galectin-3 mRNA levels were increased in most tumors compared with normal urothelium, but levels were comparable in tumors of different histological grades [10]. Kramer et al. examined the role of galectin-3 in progression of non-muscle invasive (pTa, pT1) TCC. In this study, galectin-3 was not associated with tumor grades and its loss was a valuable marker to determine development of recurrent disease [61]. Sakaki et al. reported increased serum levels of galectin-3 in bladder cancer patients compared to controls. On the other hand, there was no significant association between serum galectin-3 levels and the clinicpathological parameters, including stage and grade. Expression of galectin-3 was also found to be higher in bladder cancer tissue than that in the control tissue. They suggested that serum

galectin-3 is a marker of bladder cancer diagnosis [62]. Wang et al. reported that there was a correlation between galectin-3 expression and tumor progression and metastasis in prostate cancer. Knockdown of galectin-3 using siRNA resulted in decreased cell migration, invasion, cell proliferation, anchorage-independent colony formation, and tumor growth in the nude mouse. According to the results, they suggested that galectin-3 have the potential to serve as reliable tumor marker [63]. El Gendy et al. indicated that serum level of galectin-3 was significantly higher in patients with high-grade TCC compared with patients with low-grade tumors. They concluded that galectin-3 can be considered as a diagnostic serum marker for bladder cancers [64]. Recently, significantly increased expression and serum levels of galectin-3 was reported in patients with bladder tumors, including transitional cell carcinoma (TCC) and squamous cell carcinoma (SCC). High serum galectin-3 levels was identified as a specific marker for bladder cancer [65].

The controversial results associated with galectin-3 expression and clinicopathologic factors in various tumors could be related to tumor type, subgroup of tumor progression, technique or antibody used, and the pro- or anti-apoptotic activity of galectin-3 [66]. Galectins are potential novel therapeutic targets against different cancers, due to their involvement in cancer progression. Furthermore, anti-galectin compounds can reduce migration of cancer cells and improve effects of cytotoxic drugs. Therefore, anti-galectin compounds such as siRNAs, peptides, antibodies, and chemical inhibitors represent novel strategies for therapeutic intervention in bladder cancer [67].

5. Concluding remarks

Increased expression of galectin-3 in bladder cancer cell lines and bladder tumors has been shown to be associated with tumor progression, clinical outcome, and proliferative and apoptotic levels. The data on bladder TCCs shows a correlation between neoplastic transformation and galectin-3 expression, but there is no evidence that galectin-3 is marker of tumor progression in these cancers. A similar increase in galectin-3 has been observed in different tumors at every stage or histological grade. There is a need for alternative non-invasive and highly-efficient diagnostic methods that can replace uncomfortable cystoscopy and subjective urinary cytology. According to information presented here, expression and serum levels of galectin-3 could be useful biomarkers for diagnosis and prognosis of bladder cancer. However, future clinical studies is required to verify its diagnostic and prognostic value in bladder cancer patients. Furthermore, the role of galectin-3 in tumor progression suggests its potential as an appropriate molecular target for anticancer therapies. For example, development of galectin-3 inhibitors may be a promising therapy to combat urothelial tumors.

Acknowledgment

The authors' research is funded by Rafsanjan University of Medical Sciences.

References

[1] Khorramdelazad H et al. S100A12 and RAGE expression in human bladder transitional cell carcinoma: a Role for the Ligand/RAGE Axis in Tumor Progression? Asian Pacific J. Can. Prevent.: APJCP 2014;16(7):2725–9.
[2] N. McCarthy, Bladder cancer: Seemingly similar. Nature Reviews Cancer, 2014.
[3] A.P. Mitra, Urine cytologic analysis: special techniques for bladder cancer detection, Connection, 2010, p. 169.
[4] van den Brûle F, Califice S, Castronovo V. Expression of galectins in cancer: a critical review. Glycoconj. J. 2002;19(7–9):537–42.
[5] Hirabayashi J, Kasai K-I. The family of metazoan metal-independent β-galactoside-binding lectins: structure, function and molecular evolution. Glycobiology 1993;3(4):297–304.
[6] Elola M et al. Galectins: matricellular glycan-binding proteins linking cell adhesion, migration, and survival. Cell. Mol. Life Sci. 2007;64(13):1679–700.
[7] Wagner-Hiilsmann C et al. A galectin links the aggregation factor to cells in the sponge [Geodia cydoniuml system. Glycobiology 1996;6(8):785–93.
[8] Danguy A, Camby I, Kiss R. Galectins and cancer. Biochim et Biophysica Acta (BBA)-General Subjects 2002;1572(2):285–93.
[9] Iurisci I et al. Concentrations of galectin-3 in the sera of normal controls and cancer patients. Clin. Cancer Res. 2000;6(4):1389–93.
[10] Cindolo L et al. Galectin-1 and galectin-3 expression in human bladder transitional-cell carcinomas. Int. J. Cancer 1999;84(1):39–43.
[11] Langbein S et al. Gene-expression signature of adhesion/growth-regulatory tissue lectins (galectins) in transitional cell cancer and its prognostic relevance. Histopathology 2007;51(5):681–90.
[12] Xu X-C, El-Naggar AK, Lotan R. Differential expression of galectin-1 and galectin-3 in thyroid tumors. Potential diagnostic implications. Am. J. Pathol. 1995;147(3):815.
[13] Dumic J, Dabelic S, Flögel M. Galectin-3: an open-ended story. Biochimica et Biophysica Acta (BBA)-General Subjects 2006;1760(4):616–35.
[14] Seetharaman J et al. X-ray crystal structure of the human galectin-3 carbohydrate recognition domain at 2.1-Å resolution. J. Biol. Chem. 1998;273(21):13047–52.
[15] Saravanan C et al. Galectin-3 promotes lamellipodia formation in epithelial cells by interacting with complex N-glycans on α3β1 integrin. J. Cell. Sci. 2009;122(20):3684–93.
[16] Lau KS et al. Complex N-glycan number and degree of branching cooperate to regulate cell proliferation and differentiation. Cell 2007;129(1):123–34.
[17] Argüeso P, Panjwani N. Focus on molecules: galectin-3. Exp. Eye Res. 2011;92(1):2.
[18] Hsu DK et al. Targeted disruption of the galectin-3 gene results in attenuated peritoneal inflammatory responses. Am. J. Pathol. 2000;156(3):1073–83.
[19] Chen S-S et al. Downregulating galectin-3 inhibits proinflammatory cytokine production by human monocyte-derived dendritic cells via RNA interference. Cell. Immunol. 2015;294(1):44–53.
[20] Gao P et al. Anti-inflammatory deficiencies in neutrophilic asthma: reduced galectin-3 and IL-1RA/IL-1β. Respir. Res. 2015;16(1):5.
[21] Hsu DK, Liu F-T. Regulation of cellular homeostasis by galectins. Glycoconj. J. 2002;19(7):507–15.
[22] Henderson NC, Sethi T. The regulation of inflammation by galectin-3. Immunol. Rev. 2009;230(1):160–71.
[23] Almkvist J, Karlsson A. Galectins as inflammatory mediators. Glycoconj. J. 2002;19(7–9):575–81.
[24] Kuwabara I, Liu F-T. Galectin-3 promotes adhesion of human neutrophils to laminin. J. Immunol. 1996;156(10):3939–44.
[25] F.-T. Liu, H. Sano, D. Hsu, Monocyte Chemoattractant Activity of Galectin-3. 2005, Google Patents.
[26] Lahm H et al. Comprehensive galectin fingerprinting in a panel of 61 human tumor cell lines by RT-PCR and its implications for diagnostic and therapeutic procedures. J. Cancer Res. Clin. Oncol. 2001;127(6):375–86.
[27] Lotan R et al. Lactose-binding lectin expression in human colorectal carcinomas. Relation to tumor progression. Carbohyd. Res. 1991;213:47–57.
[28] Miyazaki J et al. Increased expression of galectin-3 in primary gastric cancer and the metastatic lymph nodes. Oncol. Rep. 2002;9(6):1307–12.
[29] Liu F-T, Rabinovich GA. Galectins as modulators of tumour progression. Nat. Rev. Cancer 2005;5(1):29–41.
[30] Califice S, Castronovo V, Van Den Brûle F. Galectin-3 and cancer (Review). Int. J. Oncol. 2004;25(4):983–1075.
[31] de Oliveira FL et al. Galectin-3 in autoimmunity and autoimmune diseases. Exper. Biol. Med. 2015. p. 1535370215593826.
[32] Peng W et al. Tumor-associated galectin-3 modulates the function of tumor-reactive T cells. Cancer Res. 2008;68(17):7228–36.
[33] Vereecken P et al. High serum galectin-3 in advanced melanoma: preliminary results. Clin. Exp. Dermatol. 2006;31(1):105–9.
[34] Vereecken P, Heenen M. Serum galectin-3 in advanced melanoma patients: a hypothesis on a possible role in melanoma progression and inflammation. J. Int. Med. Res. 2006;34(1):119–20.
[35] Zubieta MR et al. Galectin-3 expression correlates with apoptosis of tumor-associated lymphocytes in human melanoma biopsies. Am. J. Pathol. 2006;168(5):1666–75.
[36] Nangia-Makker P et al. Galectin-3 in apoptosis, a novel therapeutic target. J. Bioenerg. Biomembr. 2007;39(1):79–84.
[37] Nangia-Makker P et al. Inhibition of human cancer cell growth and metastasis in nude mice by oral intake of modified citrus pectin. J. Natl. Cancer Inst. 2002;94(24):1854–62.
[38] Johnson KD et al. Galectin-3 as a potential therapeutic target in tumors arising from malignant endothelia. Neoplasia 2007;9(8):662–70.
[39] Thijssen VL et al. Galectin expression in cancer diagnosis and prognosis: a systematic review. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 2015;1855(2):235–47.
[40] Flotte TJ, Springer T, Thorbecke G. Dendritic cell and macrophage staining by monoclonal antibodies in tissue sections and epidermal sheets. Am. J. Pathol. 1983;111(1):112.
[41] Sanjuan X et al. Differential expression of galectin 3 and galectin 1 in colorectal cancer progression. Gastroenterology 1997;113(6):1906–15.

[42] Puglisi F et al. Galectin-3 expression in non-small cell lung carcinoma. Cancer Lett. 2004;212(2):233–9.
[43] Califice S et al. Dual activities of galectin-3 in human prostate cancer: tumor suppression of nuclear galectin-3 vs tumor promotion of cytoplasmic galectin-3. Oncogene 2004;23(45):7527–36.
[44] de Oliveira JT, Ribeiro C, Gärtner F. Role of galectin-3 in cancer metastasis. Glycobiol. Insights 2015;5:1.
[45] Faba OR, Palou J. Predictive factors for recurrence progression and cancer specific survival in high-risk bladder cancer. Curr. Opin. Urol. 2012;22(5):415–20.
[46] Ho M-K, Springer T. Mac-2, a novel 32,000 Mr mouse macrophage subpopulation-specific antigen defined by monoclonal antibodies. J. Immunol. 1982;128(3):1221–8.
[47] Leffler H, Masiarz FR, Barondes SH. Soluble lactose-binding vertebrate lectins: a growing family. Biochemistry 1989;28(23):9222–9.
[48] Raz A et al. Molecular cloning and chromosomal mapping of a human galactoside-binding protein. Cancer Res. 1991;51(8):2173–8.
[49] Cheng D, Liang B, Li Y. Serum Galectin-3 as a Potential Marker for Gastric Cancer. Med. Sci. Monit.: Int. Med. J. Exper. Clin. Res. 2015;21:755.
[50] Xue G et al. *[Detection of galectin-3 in both serum and tissue for early diagnosis of thyroid carcinoma].* Nan fang yi ke da xue xue bao=. J. South. Med. Univ. 2013;33(7):1027–30.
[51] Takenaka Y, Fukumori T, Raz A. Galectin-3 and metastasis. Glycoconj. J. 2002;19(7–9):543–9.
[52] Nakahara S, Oka N, Raz A. On the role of galectin-3 in cancer apoptosis. Apoptosis 2005;10(2):267–75.
[53] Calvier L et al. Galectin-3 mediates aldosterone-induced vascular fibrosis. Arterioscler. Thromb. Vasc Biol. 2013;33(1):67–75.
[54] Chen C et al. Increased circulation of galectin-3 in cancer induces secretion of metastasis-promoting cytokines from blood vascular endothelium. Clin. Cancer Res. 2013;19(7):1693–704.
[55] Liu J et al. Vascular endothelial growth factor C enhances cervical cancer cell invasiveness via upregulation of galectin-3 protein. Gynecol. Endocrinol. 2014;30(6):461–5.
[56] Song L et al. Galectin-3 in cancer. Clin. Chim. Acta 2014;431:185–91.
[57] Yang R-Y, Hsu DK, LIu F-T. Expression of galectin-3 modulates T-cell growth and apoptosis. Proc. Natl. Acad. Sci. 1996;93(13):6737–42.
[58] Bichara M et al. Exploring the role of galectin 3 in kidney function: a genetic approach. Glycobiology 2006;16(1):36–45.
[59] Hsu DK, Chen HY, Liu FT. Galectin-3 regulates T-cell functions. Immunol. Rev. 2009;230(1):114–27.
[60] Francois C et al. Galectin-1 and galectin-3 binding pattern expression in renal cell carcinomas. Am. J. Clin. Pathol. 1999;112(2):194–203.
[61] Kramer MW et al. Decreased expression of galectin-3 predicts tumour recurrence in pTa bladder cancer. Oncol. Rep. 2008;20(6):1403.
[62] Sakaki M et al. Serum level of galectin-3 in human bladder cancer. J. Med. Invest. 2008;55(1,2):127–32.
[63] Wang Y et al. Regulation of prostate cancer progression by galectin-3. Am. J. Pathol. 2009;174(4):1515–23.
[64] El Gendy H et al. Galectin 3 for the diagnosis of bladder cancer. Arab J. Urol. 2014;12(2):178–81.
[65] Gendy H et al. Diagnostic and prognostic significance of serum and tissue galectin 3 expression in patients with carcinoma of the bladder. Curr. Urol. 2013;7(4):185–90.
[66] Canesin G et al. Galectin-3 expression is associated with bladder cancer progression and clinical outcome. Tumor Biol. 2010;31(4):277–85.
[67] Ingrassia L et al. Anti-galectin compounds as potential anti-cancer drugs. Curr. Med. Chem. 2006;13(29):3513–27.