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Galectins and Urological Cancer

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Abstract Galectins are a family of proteins defined by their affinity for β-galactoside and by their conserved sequence. Each galectins exhibits a specific expression pattern in various tissues and their expression is regulated during development. Their expression is altered in many types of cancers and non-cancerous disorders. They interact with glycoproteins in both extracellular and intracellular milieu and regulate various biological phenomenon including cell growth, cell differentiation, cell adhesion, and apoptosis. A series of experimental and clinical evidences have been reported to support correlation between galectin expressions and neoplastic transformation. The recent findings show that expressions of galectins are elevated with neoplastic progression in certain malignancies, and therefore, galectins are expected to serve as reliable tumor markers. In this review, we describe the expression and role of galectins in urological cancers and their clinical applications for diagnostic and therapeutic use. J. Cell. Biochem. 91: 118–124, 2004.

Key words: galectins; urological cancer

Galectins are a family of proteins defined by their affinity for β-galactosides and by conserved sequence elements [Barondes et al., 1994]. At present, 14 galectins from mammals are known. Each members of the galectin family contains at least one carbohydrate recognition domain (CRD). Galectins are classified into three groups, based on the content and organization of domains [Perillo et al., 1998; Dunphy et al., 2002]. The prototype galectins (galectin-1, -2, -5, -7, -10, -11, -13, and -14) consist of a CRD. The tandem repeat galectins (galectin-4, -6, -8, -9, and -12) consists of two CRDs. The chimera galectin (galectin-3) consists of one CRD, N-terminal domain and intervening proline, glycine-rich domain.

Galectins exist in intracellular and extracellular milieu. They can shuttle between cytoplasm and nucleus and be secreted by non-classical pathway [Danguy et al., 2002]. In the extracellular space, they link with β-galactoside containing glycoconjugates of extracellular matrix (ECM) components and cell surface adhesion molecule (Table I). The bindings of galectins to ECM components and cell surface adhesion molecules regulate cell adhesion and differentiation [Hikita et al., 2000; Hughes, 2001]. In the intracellular space, galectins bind to their ligands via not only lectin–glycoconjugate interaction but also protein–protein interaction (Table II). There, galectins regulate mRNA splicing, cell cycle, apoptosis, and cell proliferation.

In certain types of cancers, the expression of galectins is positively correlated to tumor progression. In other types of cancers, it is inversely correlated to tumor progression (Table III). Thus, levels of galectins expression depend on the organ or tissue, suggesting that tissue specific factors may modulate the expression and functions of galectins.

Urological cancer is among the most morbid of human malignancies. The estimated new cases of urological cancers for 2003 are 310,000 cases in USA [Ries et al., 2003]. Although improvement of diagnostic procedures has enabled us to detect very small cancers, the estimated deaths by urological cancers for 2003 are as much as

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TABLE I. Extracellular Ligands for Galectins

Ligands	Reference
Galectin-1	
Carcinoembryonic antigen	[Ohannesian et al., 1994]
Laminin	[Zhou and Cummings, 1993]
Fibronectin	[Zhou and Cummings, 1993]
Thy-1 antigen	[Symons et al., 2000]
CD45	[Symons et al., 2000]
α7β1 Integrin	[Gu et al., 1994]
Complement receptor CR3	[Avni et al., 1998]
Lamp-1, -2	[Ohannesian et al., 1994]
Galectin-3	
Carcinoembryoninc antigen	[Ohannesian et al., 1995]
Laminin	[Sato and Hughes, 1992]
Fibronectin	[Sato and Hughes, 1992]
Tenascin	[Probstmeier et al., 1995]
Mac-2 binding protein	[Rosenberg et al., 1991]
Neuronal adhesive glycoprotein L1	[Probstmeier et al., 1995]
N-CAM	[Probstmeier et al., 1995]
Myelin-associated protein	[Probstmeier et al., 1995]
NCA 160	[Yamaoka et al., 1995]
β1 Integrin	[Ochieng, 2001]
TCR complex	[Demetriou et al., 2001]
Galectin-8	
α3β1 Integrin	[Hadari et al., 2000]

TABLE III. Correlation Between Galectins Expression and Tumor Progression

Tissue	Reference
Positive correlation	
Galectin-1	
Thyroid	[Xu et al., 1995]
Uterine sarcoma	[Schwarz et al., 1999]
Galectin-3	
Gastric cancer	[Lotan et al., 1994]
Liver cancer	[Hsu et al., 1999]
Thyroid	[Xu et al., 1995; Inohara et al., 1999; Bartolazzi et al., 2001]
Negative correlation	
Galectin-1	
Head and neck cancer	[Choufani et al., 1999]
Galectin-3	
Head and neck cancer	[Choufani et al., 1999]
Uterine sarcoma	[Schwarz et al., 1999]
Breast	[Castronovo et al., 1996]
Pancreas cancer	[Shimamura et al., 2002]
Galectin-8	
Colon	[Nagy et al., 2002]
Conflicting data	
Galectin-3	
Colon	[Lotz et al., 1993; Schoeppner et al., 1995; Ma and Geng, 2002]

54,000, due to the limitations of the therapeutic procedures. The efficacy of various currently available therapeutic strategies including chemotherapy, radiotherapy, and immunotherapy is not always sufficient, especially for the advanced or recurrent disease. Therefore, new methods for cancer therapy have been sought. Recently, advances in molecular biology have led to novel approaches for cancer treatment.

In this review, we focus on galectins expression and their roles in urological disorders, especially urological cancers.

GALECTINS IN NORMAL DEVELOPMENT AND NON-CANCEROUS DISORDERS

Expression of galectins and their roles in normal development have been examined by immunohistochemical analysis and in vitro experiments using MDCK cells, which form tubes and cysts in 3D culture.

TABLE II. Intracellular Ligands for Galectins

Ligands	References
Galectin-1	
Gemin 4	[Park et al., 2001]
H-Ras	[Paz et al., 2001]
Galectin-3	
Alix/AIP-1	[Liu et al., 2002]
Bcl-2	[Yang et al., 1996]
CBP70	[Seve et al., 1994]
Chrp	[Menon et al., 2000]
Cytokeratin	[Karsten, 1997]
Gemin 4	[Park et al., 2001]
Synexin	[Yu et al., 2002]

Expression of galectin-1 was developmentally regulated in testis and stage specific expression pattern was observed throughout the spermatogenic process. In adult normal testis, galectin-1 but not galectin-3 was expressed in Sertoli cells. On the other hand, Sertoli cells in normal testis had binding sites for both galectins [Timmons et al., 2002; Dettin et al., 2003]. In Sertoli cells of Sertoli cell only-syndrome (SCOS), galectin-3 was expressed and galectin-1 specific binding sites were increased, indicating the involvement of galectins in pathogenesis of SCOS [Wollina et al., 1999].

Several reports indicated the significance of galectin-3 in development and pathogenesis of kidney. MDCK cells suspended in Matrigel exhibited differential and polarized galectin-3 expression on the baso-lateral surface domains of cells lining the cysts [Bao and Hughes, 1995]. In tubule-forming cysts, galectin-3 is excluded from the initial spikes and the progressing tips of the tubules, although its basolateral expression on the cyst body remains. Galectin-3 added exogenously to cultures exerted an inhibitory effect on cyst enlargement of MDCK cells while galectin-3-specific antibodies could promote this process. These results indicate that galectin-3 interacts with glycosylated surface

receptors and acts as a negative growth regulator in the development of MDCK cysts.

Galectin-3 affects not only epithelial cells of kidney but also mesangial cells. Exogenous galectin-3 protects mesangial cells from cytotoxicity of TGF-β and serum starvation and induces matrix synthesis [Sasaki et al., 1999].

The growth regulatory effect of galectins on kidney cells as well as immunosuppressive effect of galectins contributes to pathogenesis of kidney disorders. Several experiments employing animal models revealed the involvement of galectin-3 in non-cancerous disorders of kidney. Galectin-3 works as a mediator of bacterial adherence to kidney cells, implicating the involvement of galectin-3 in urinary tract infections [Altman et al., 2001]. Galectin-3 expression in mesangium is induced by diabetic milieu and it inhibits glomerulopathy by interacting with advanced glycation end products [Pugliese et al., 2000, 2001]. Galectin-1, -3, and -9 inhibited immune-mediated glomerular diseases [Tsuchiyama et al., 2000]. Galectin-3 expressions were markedly up-regulated in acute renal failure [Nishiyama et al., 2000].

GALECTINS IN DIAGNOSIS AND PROGNOSIS OF UROLOGICAL MALIGNANCY

To date, a series of experimental and clinical evidences have been reported to support correlation between galectin expressions and neoplastic transformation. Consequently, diagnostic and prognostic relevance of galectins have been shown, though there are still some conflicting data regarding a certain type of tumor tissues. The recent findings show that expressions of galectins are elevated with neoplastic progression in certain malignancies, and therefore, galectins are expected to serve as reliable tumor markers.

Here we describe possible involvement of galectins in urological malignancy.

Prostate

The expression of galectin-1 was examined in 148 human primary prostate carcinoma samples [Van den Brule et al., 2001]. Immunohistochemical staining of paraffin sections of prostate tissues revealed that galectin-1 was not detected in normal, intraepithelial neoplasia or carcinoma cells, but accumulated in the stroma and associated fibroblasts. The association between accumulation of galectin-1 in the stroma of the malignant tissue and aggressiveness of the tumor emphasizes the evidence that identifies a role for galectin-1 in the acquisition of the invasive phenotype [Van den Brule et al., 2001].

The expression of galectin-3 was also examined in a population of 145 prostate carcinoma samples using immunohistochemistry [Van den Brule et al., 2000]. Most of the non-tumoral prostatic glands exhibited moderate immunostaining for galectin-3 localized in both nucleus and cytoplasm. In prostatic cancer cells, galectin-3 was usually not expressed or decreased compared with the normal glands. Interestingly, when galectin-3 was detected in the cancer cells, it was consistently excluded from the nucleus and only present in the cytoplasmic compartment Van den Brule et al. [2000].

Regarding the expression of galectin-8 in the prostate, there have been conflicting data reported so far [Su et al., 1996; Danguy et al., 2001]. On the one hand, galectin-8 is selectively expressed in prostatic cancer cells but not in normal prostate or benign hyperplasia [Su et al., 1996] whereas, on the other hand, galectin-8 is expressed at very low levels in normal tissues as well as in benign hyperplasia or adenocarcinomas [Danguy et al., 2001]. Evaluation of a large number of prostate biopsy specimens will be needed to provide a better understanding of this endolectin.

Bladder

The expression of galectin-1 and galectin-3 was investigated in 38 human bladder transitional cell carcinomas of different histological grade and clinical stage and in five normal urothelium samples [Cindolo et al., 1999]. Galectin-1 mRNA levels were highly increased in most high-grade tumors compared with normal bladder or low-grade tumors. Western blot and immunohistochemical analysis of normal and neoplastic tissues revealed a higher content of galectin-1 in tumors. Galectin-3 mRNA levels were also increased in most tumors compared with normal urothelium, but levels were comparable among tumors of different histological grade [Cindolo et al., 1999].

In regard to galectin-8 expression, no significant differences were observed between normal cases and transitional carcinomas. However, the low number of specimens and the heterogeneity of the immunostaining prevent any final conclusion [Danguy et al., 2001].

Kidney

Renal cell carcinomas (RCCs) are characterized by an unpredictable clinical course. Therefore, a better understanding of the biologic and molecular cell changes associated with the development of this disease is needed. The level of expression of galectin-1 and galectin-3 and their respective binding sites in a series of 74 RCCs were characterized [Francois et al., 1999]. The results showed that the level of expression of galectin-1 binding sites is significantly lower in grade II+/III+ than in grade II−/III− RCCs. The increase in biologic aggressiveness seems to be paralleled by a decrease in the level of expression of galectin-1 binding sites rather than by a decrease in the level of expression of galectin-1 itself. A similar conclusion is true for galectin-3 [Francois et al., 1999]. The cDNA microarray and immunohistochemical experiments showed that the expression of galectin-3 appeared to correlate with tumor indolence; being expressed predominantly in low-grade conventional (clear cell) RCCs, indolent chromophobe RCCs, and benign oncocytomas [Young et al., 2001]. This finding is consistent with several studies showing reduced galectin-3 expression in clinically aggressive tumors and may be relevant to the function of galectin-3 as an adhesion molecule that inhibits metastasis [Idikio, 1998; Francois et al., 1999; Lurisci et al., 2000; Pacis et al., 2000]. Thus, galectins represent a family of molecules with a key role in RCCs progression. With the expression of galectin-8, no statistically significant differences in the staining score were observed between the normal specimens and the renal cell carcinomas [Danguy et al., 2001].

EFFECT OF GALECTINS ON UROLOGICAL TUMOR CELL LINES

Effects of galectins on prostate cancer cells were examined using galectin-1, galectin-3 null prostate cancer cell line, LNCaP [Ellerhorst et al., 1999, 2002]. Treatment of LNCaP cells with differentiation-inducing reagent, sodium butyrate resulted in induction of galectin-1 expression, inhibition of proliferation, morphologic changes consistent with a differentiated phenotype, and induction of apoptosis [Ellerhorst et al., 1999]. Galectin-1 transfected LNCaP cells displayed growth inhibition and an increased rate of apoptosis. These results suggest that galectin-1 functions downstream in the pathway of butyrate-induced differentiation and negatively regulates growth of prostate cancer cells.

Galectin-3 has the similar role to galectin-1. Transfection of galectin-3 into LNCaP cells resulted in in vitro and in vivo growth inhibition [Ellerhorst et al., 2002]. Galectin-3 transfected cells proliferate at a slower rate in vitro than the vector control-transfected lines. When injected subcutaneous in nude mice, galectin-3 transfected cells formed tumors at a slower rate than control cells. In contrast to the stimulatory role in many tumor types, galectin-1 and galectin-3 is the inhibitory molecules for prostate cancer.

CLINICAL APPLICATION

Expression pattern of galectins, especially galectin-3, is altered in many types of cancers. Therefore, several attempts to use galectin-3 expression as a diagnostic indicator are under development. Iurisci et al. [2000] showed that galectin-3 serum levels in patients with cancer were significantly elevated compared with healthy individuals. Inohara et al. [1999] demonstrated that expression of galectin-3 in fine needle aspirates could be a diagnostic marker for thyroid cancer. Because down-regulation of galectin-3 is associated with clinical aggressiveness in urological cancers, level of galectin-3 in biopsy specimens can be a useful prognostic marker.

Concerning the cancer treatment, galectin-3 is one of the targeting proteins. Galectin-3 is involved in several steps of metastasis, including angiogenesis [Nangia Makker et al., 2000], tumor embolism formation [Inohara and Raz, 1994], resistance to suspension induced apoptosis [Yoshii et al., 2002], and tumor cell attachment to endothelial cells [Glinsky et al., 2000]. These functions of galectin-3 make it a likely therapeutic target. John et al. [2003] showed that NH2-terminally truncated galectin-3, which competes with endogenous galectin-3, inhibits in vivo tumor growth and metastasis. We have been reported that pH-modified citrus pectin (MCP) inhibits in vivo tumor growth and spontaneous metastasis [Platt and Raz, 1992; Pienta et al., 1995; Nangia-Makker et al., 2002]. Pectin is a highly complex branched polysaccharide fiber rich in galactoside residues and present in all plant cell walls. Although citrus pectin (CP) is unable to interact with galectin-3, it acts as a ligand

for galectin-3 in its modified form (MCP) after hydrolysis to form a smaller linear water-soluble fiber. MCP is reported to inhibit galectin-3 mediated homotypic aggregation of tumor cells in vitro [Inohara and Raz, 1994] and galectin-3 mediated angiogenesis in vitro [Nangia Makker et al., 2000]. Moreover, oral administration of MCP inhibited spontaneous metastasis of rat prostate cancer cells. Recent study has revealed that galectin-3 null mutant mice are relatively healthy, suggesting that galectin-3 inhibitors, like MCP and truncated galectin-3, may be therapeutically valuable without causing severe side effects.

CONCLUSIONS

Numerous data demonstrate that certain alterations of cell surface carbohydrates and lectins are associated with cancer progression and metastasis. Here, we reviewed the expression of galectins, β-galactoside binding lectins, in urological cancers. In contrast to other types of cancers, expression of galectin-3 is down-regulated in urological cancers, suggesting that galectin-3 has a tumor suppressive role in urological organs. The mechanism by which galectin-3 promotes cancer progression have been reported. However, little is known about tumor suppressive functions of galectin-3. To clarify the functions of galectins, assessment of the natural functional galectins ligands on tumor cells and stroma cells will be required. Furthermore, it is important to investigate the intracellular signaling caused by galectins. Answering these questions should progress our understanding of galectins as well as that of cancer progression.

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