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