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Review

Role of the interaction between galectin-3 and cell adhesion molecules in cancer metastasis

Ming Xin, Xin-Wen Dong, Xiu-Li Guo *

Department of Pharmacology, School of Pharmaceutical Sciences, Shandong University, Jinan 250012, China

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ABSTRACT

Galectin-3, a unique chimera-type member of the β-galactoside-binding soluble lectin family, is present in both normal and cancer cells and plays a crucial role in the regulation of cell adhesion. It is involved both in accelerating detachment of cells from primary tumor sites and promoting cancer cell adhesion and survival to anoikis in the blood stream. Cell adhesion molecules (CAMs) are membrane receptors that mediate cell–cell and cell–matrix interactions, and are essential for transducing intracellular signals responsible for adhesion, migration, invasion, angiogenesis, and organ-specific metastasis. This review will discuss the recent advances in our understanding the biological functions, mechanism and therapeutic implication of the interaction between galectin-3 and CAMs in cancer metastasis.

1. Introduction

Galectin-3, a pleiotropic β-galactoside-binding protein, contains an evolutionary conserved sequence element of carbohydrate-recognition domain (CRD) which is characterized by specific binding of β-galactosides and an *N*-terminal domain through which forms oligomers. This protein distributes inside and outside the cell and has diverse biological functions, such as cell growth, cell adhesion, cell–cell interaction, and RNA processing in a specific situation [1]. In extracellular compartment or on cell membrane surface, it has long been suspected of regulating cellular adhesion in a novel fashion. For example, overexpression of galectin-3 enhances tumor cell adhesion to extracellular matrix (ECM) and favours the escape of tumor cells from the primary tumor sites [2].

Adhesion is one of the common tumor cellular development processes that including migration of tumor cells within the primary site, intravasation into blood or lymphatic vessels, survival and dissemination in the circulation, adherence to vascular endothelial cells at secondary sites, extravasation, colonization, and population to form micro- to macro-metastatic foci. To complete the metastatic cascade, a tumor cell utilizes enhanced plasticity in the interactions with adjacent tumor cells, ECM, and other cell types within the microenvironment. Cell adhesion molecules (CAMs) are an important regulator for this homotypic and heterotypic interactions [3].

CAMs are a group of proteins located on the cell surface, which are involved in the binding events of cells to one another or to ECM. All CAMs are integral membrane proteins that have cytoplasmic, transmembrane and extracellular domains. The cytoplasmic tail often interacts with cytoskeletal proteins, which serve as the actual anchor within the cells. Many families including cadherins, selectins, integrins, the immunoglobulin superfamily (Ig-SF), and lymphocyte homing receptors, such as CD44 belong to CAMs [4]. Apart from these CAM proteins, the mucoprotein 1 (Muc1), which is not generally defined as CAMs, also plays an important role in adhesion.

A mass of studies have been performed with the aim to clarify the interaction between galectin-3 and CAMs [5–7]. Many new points have been raised, for example, the expression level of galectin-3 correlates with the biological function of integrin; galectin-3 could regulate E-cadherin expression via interaction with β-catenin; galectin-3 colocalizes with *N*-cadherin and regulates its expression to modulate vasculogenic mimicry (VM); galectin-3 could bind to muc1 via Thomsen–Friedenreich glycoantigen (TFAg or TF antigen) to regulate the cellular adhesion by exposing the cadherin molecules on the cell surface, etc. In this review, we will discuss recent developments in the understanding of the relation of galectin-3 and CAMs, their biological functions and possible mechanisms in cancer metastasis. In addition, the clinical significance in cancer treatment will also been discussed.

* Corresponding author. Department of Pharmacology, School of Pharmaceutical Sciences, Shandong University, No. 44 Wen Hua Xi Road, Jinan 250012, PR China. Tel.: +86 531 8838 2490; fax: +86 531 8838 2490.
E-mail address: guoxl@sdu.edu.cn (X.-L. Guo).

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2. Galectin-3 and integrin

Integrins are a family of heterodimeric transmembrane receptors for components of the ECM, such as fibrinogen (FN), laminin (LN), collagen (Col), and vitronectin (VN). In mammals, eighteen α-subunits and eight β-subunits are paired to form 24 different integrins. Each pair of α-subunits and β-subunits has a defined set of ECM ligands in a cell type-specific manner [8]. Integrins cluster in specific cell–matrix adhesions to provide dynamic links between extracellular and intracellular environments by bi-directional signalling and by organizing the ECM and intracellular cytoskeletal and signalling molecules. Through bi-directional "outside-in" and "inside-out" signalling, integrins regulate multiple biological processes, such as adhesion, apoptosis, proliferation, differentiation, migration, and metastasis [9]. Galectin-3 is known to bind to LN, Lamp I and II, IgE and Mac-2 binding proteins. In addition, galectin-3 can also mediate the cell adhesion to ECM by regulating integrins [5]. Galectin-3 may regulate tumor cell migration and invasion by promoting integrin clustering on the cell surface, mediating the endocytosis of integrins or activating integrin directly [10,11].

2.1. Galectin-3 mediates the endocytosis of integrins by tumor cells

The association of solute transporters and receptors with components of the endocytic machinery could regulate their surface levels, and thereby cellular sensitivity to ligands, cytokines and nutrients in the extracellular environment. It has been shown that galectin-3 and β1 integrins are internalized into MDA-MB-231 breast carcinoma cells via a cavaleolae-like pathway of endocytosis causing β1 integrins not available for firm adhesion [12].

The endocytosis of integrins is mainly related with the concentration of the galectin-3. The concentration of the galectin-3 in the extracellular microenvironment of cells in *vivo* or in culture is sufficient for trafficking and redistribution of integrins on the cell surface thereby remodelling the cytoskeleton and modulating cell spreading and adhesion. The moderate levels of extracellular galectin-3 could also be involved in the remodelling of adhesion plaques containing other integrins, such as αvβ3 which are critical in the process of angiogenesis. However, high concentrations of galectin-3 may interfere with integrin heterodimer, in such a way to limit integrin expression on the cell surface [2,12].

2.2. Galectin-3 promotes integrin clustering on the cell surface by ligating the glycosylated cell surface molecules (CD98, EGFR)

Studies have characterized ancillary membrane proteins that interact with the cytoplasmic tails of integrin subunits and can indirectly recruit signalling molecules, such as non-receptor kinases into the adhesive complex. One of these proteins is glycosylated cell surface molecule, CD98 antigen, a galectin-3 ligand [13]. Galectin-3 ligates CD-98 molecule which in turn mediates integrin clustering on the cell surface to increase the avidity of binding CD-98 heterodimers, comprised of a heavy chain (CD-98hc, SLC3A2) and a light chain. CD-98 interacts with integrins through CD-98hc chain. CD98hc overexpression leads to anchorage-independent cell growth and tumorigenesis in 3T3 fibroblasts and activates certain integrin-regulated signalling pathways. Furthermore, CD98hc is required for efficient adhesion-induced activation of Akt and Rac GTPase, which are major contributors to the integrin-dependent signals involved in cell survival and cell migration [14]. CD-98 is highly expressed in many cancers and contributes to tumors formation in experimental models. What is more, vertebrates, which possess highly conserved CD-98 proteins and CD-98-binding integrins, also display propensity towards invasive and metastatic tumors [15].

In addition, researches suggest that the cooperation between integrin and growth factor receptors (GFR) or receptor tyrosine kinases regulates certain signalling functions, which are important for cancer progression [16]. Galectin-3 binding with epidermal growth factor receptor (EGFR) could reduce EGFR trafficking into clathrin-coated pits and caveolae lipid rafts, decrease ligand-independent receptor activation and promote α5β1 integrin remodelling in focal adhesions [17]. Additionally, Boscher et al. found that Mgat5 (*N*-acetylglucosaminyltransferase V)-dependent galectin-3 lattice enables galectin-3 to promote EGF signal transduction, which induces galectin-3-dependent integrin activation. Then, the active integrin triggers Src-dependent phosphorylation of Caveolin1 and RhoA/ROCK signalling, leading to actin and matrix remodelling and tumor cell metastasis [18].

2.3. Galectin-3 directly modulates some integrins activation

In many cases, integrins bind to their extracellular ligands relatively weakly and need to undergo conformational changes to achieve high-affinity. External factors, such as divalent cations, or certain monoclonal antibodies reacting with extracellular domains of integrin subunits, may modulate integrin affinity for ligands. Preliminary evidence suggests that galectin-3, through binding to extracellular domains of integrin, may modulate positively or negatively integrin activation, and regulate its binding with extracellular ligands [13]. Galectin-3 expression enhances β1 integrin-mediated cell adhesion to fibronectin (FN) and laminin (LN), as well as cell migration. In turn, β1 integrin induces galectin-3 expression by demethylation of the Lgals3 promoter, which promotes cell migration. The functional feedback-loop between β1 integrins and galectin-3 involves in the epigenetic induction of galectin-3 expression during integrin-induced EMT and cell scattering [19]. However, Friedrichs et al. found that galectin-3 weakened integrin α2β1-mediated adhesion of Madin–Darby canine kidney (MDCK) cells to collagen-I or -IV. The adhesion reduction was specific to intergrain α2β1, as it was not observed when MDCK cells adhered to ECM substrate by other integrins [20].

2.4. α1β1 and CDIIb/18 integrin interact with galectin-3 directly

α1β1 and CDIIb/18 are two members of the integrin family. Ochieng et al. has shown that α1β1 and CDIIb/18 integrin can interact directly with galectin-3 through CRD of galectin-3 binding to the tri- and tetra-antennary branches of polylactosamine residues on the integrins. Galectin-3 can also bind to FN, LN, Col and VN as multifunctional modulators of cell adhesion [2]. Galectin-3 may suppress or enhance the cell adhesions, and may operate through a number of different mechanisms (Fig. 1).

At high in *vivo* extracellular concentration of galectin-3, monovalent binding would be expected for many prototypic galectins, and for the dimeric prototypic galectins or tandem galectins when these are present in large excess relative to the cell surface or matrix molecules. Galectin-3 fails to modulate adhesion of tumor cells to FN or LN. The binding interaction is presumed to either alter the affinities or by steric hindrance negate the binding of integrins to their ECM ligands [5,13]. In addition, as previously mentioned, galectin-3 might induce the endocytosis of integrins [12]. At low amount compared with ligand concentration, a bivalent galectin-3 binding simultaneously to cell surface and matrix receptors acts synergistically in cell–cell adhesions and cell–matrix adhesions [5].