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New Drugs

Unraveling galectin-1 as a novel therapeutic target for cancer

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SUMMARY

Galectins belong to a family of carbohydrate-binding proteins with an affinity for β-galactosides. Galectin-1 is differentially expressed by various normal and pathologic tissues and displays a wide range of biological activities. In oncology, galectin-1 plays a pivotal role in tumor growth and in the multistep process of invasion, angiogenesis, and metastasis. Evidence indicates that galectin-1 exerts a variety of functions at different steps of tumor progression. Moreover, it has been demonstrated that galectin-1 cellular localization and galectin-1 binding partners depend on tumor localization and stage. Recently, galectin-1 overexpression has been extensively documented in several tumor types and/or in the stroma of cancer cells. Its expression is thought to reflect tumor aggressiveness in several tumor types. Galectin-1 has been identified as a promising drug target using synthetic and natural inhibitors. Preclinical data suggest that galectin-1 inhibition may lead to direct antiproliferative effects in cancer cells as well as antiangiogenic effects in tumors. We provide an up-to-date overview of available data on the role of galectin-1 in different molecular and biochemical pathways involved in human malignancies. One of the major challenges faced in targeting galectin-1 is the translation of current knowledge into the design and development of effective galectin-1 inhibitors in cancer therapy.

Introduction

Galectins are β-galactoside-binding proteins characterized by their interaction with polylactosamine moieties located on glycoproteins or glycolipids [1]. They show a high level of evolutionary conservation, having been identified in many species from nematodes to mammals, with 15 mammalian galectins identified to date. The galectin family is defined by a consensus amino acid sequence and the presence of at least one conserved carbohydrate-recognition domain (CRD) which is responsible for its binding to N- and O-linked glycans [2]. Three groups have been identified, those with one CRD (galectins 1, 2, 5, 7, 10, 11, 13, 14, 15), those with two homologous CRDs connected by a short linker peptide (galectins 4, 6, 8, 9 12), and galectin-3, the only galectin bearing one CRD fused to tandem repeats of short amino-acid stretches [1]. While galectins harboring one CDR can form dimers allowing binding to two carbohydrates, galectin-3 can form oligomers when bound to multivalent carbohydrates [3]. Each member of this family displays different glycan-binding properties, mainly in the recognition of sialyled and sulphated glycans, which could explain the differences in their biological activities [4–6], along with intrinsic and extrinsic factors such as oligomerization status and active remodeling of N- and O-glycans in target cells [7].

Galectins have a wide range of biological functions in several different processes including homeostasis, apoptosis, and vascular embryogenesis [8–13] and in pathological conditions such as pre-eclampsia, inflammation, diabetes, atherosclerosis, and cancer [14–17]. There is extensive evidence that galectins are found both extracellularly [18] and intracellularly, in the cytosol and nucleus

Abbreviations: Gal-1, galectin-1; PI3K, phosphoinositide-3-kinase; MEK, mitogen-activated protein kinase kinase (MAP2K); ERK, extracellular-signal-regulated kinase; ECM, extracellular matrix; MMP, matrix metalloproteinase; tPA, tissue plasminogen activator; CDC42, cell division control protein 42 homolog; RhoA, Ras homolog gene family, member A; PKC, protein kinase C; JNK, c-Jun NH2-terminal kinases; NRP1, neuropilin-1; VEGFR2, vascular endothelial growth factor receptor 2; ROS, reactive oxygen species; NFkB, nuclear factor kappa B; HIF1α, hypoxia-inducible factor 1-alpha.

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[19]. Interestingly, some galectins are distributed in a wide variety of tissues whereas others display high tissue-specificity [20].

Several lines of evidence have been identified showing that galectins strongly influence tumor progression via their effects on immune surveillance, angiogenesis, cell migration, tumor cell adhesion, and cellular response to chemotherapy [3]. These observations are reinforced by a large body of work indicating that galectins, and in particular galectin-1, play key roles in multiple aspects of cancer biology and that galectin expression correlates with tumor aggressiveness and progression in numerous human neoplasias [3]. Here we review the major biological roles of galectin-1 in the hallmark of cancer progression in view of the future use of galectin-1 inhibitors as novel cancer therapies.

Galectin-1

Galectin-1 is encoded by the *LGALS1* gene located on chromosome 22q12 [21]. The methylation status of the promoter is a key mechanism regulating galectin-1 expression [22,23] Furthermore, several transcription factors are implicated in galectin-1 expression such as hypoxia inducible factor-1 (HIF-1) in colorectal cancer cells [24], nuclear factor κ B (NFκB) in T cells [25] and Kaposi's sarcoma [26], activator protein 1 (AP1) in classical Hodgkin lymphoma Reed-Sternberg cells [27] and CAAT/enhancer binding prot α (C/EBPα) in acute myeloid leukemia [28].

Galectin-1 is a 14 KDa monomer or a non-covalent homodimer with one CRD per subunit [21]. The presence of more than one CRD in the homodimer makes it suitable for mediating cell adhesion, triggering intracellular signaling and forming multivalent lattices with cell surface glycoconjugates [29]. In the extracellular space, homodimers can link several membrane receptors facilitating cell signaling and cell–cell interactions allowing homotypic and heterotypic aggregation [21]. Galectin-1 is involved in numerous physiologic processes including neural stem cell growth, hematopoietic lineage differentiation and muscle differentiation [21,30]. In addition, compelling evidence amassed over recent decades indicates that galectin-1 upregulation can dramatically influence tumor progression given its pleiotropic roles in cell transformation [31], cell proliferation [21,32], angiogenesis [14,33], cell adhesion and invasiveness [34–37], and immunosuppression [38,39].

Each galectin-1 monomer contains six cysteine residues per subunit, conferring a strong sensitivity to oxidation [40,41]. The cysteine residues must be in a reduced state to maintain a molecular structure with lectin activity, since oxidized galectin-1 lacks it lectin activity [42]. Furthermore, oxidized galectin-1 was shown to have cytokine-like behavior [43,44]. During oxidation, intramolecular disulfide bridges form on the galectin-1 structure induce deep conformational changes, which prevents its dimerization and ligand recognition [42,45]. The presence of galectin-1 ligands induces a shift in the monomer–dimer equilibrium favoring its dimerization and protecting galectin-1 from oxidation [46].

Intracellular galectin-1 is found in the nucleus, cytoplasm, and the inner leaflet of the cytoplasmic membrane [47]. Like the other members of this family, galectin-1 is secreted into the extracellular space despite lacking signaling sequences required for secretion via the standard endoplasmic reticulum/Golgi pathway [48]. Extracellular galectin-1 has a slightly higher molecular weight (~15 kDa) than the 14 kDa form found in cell lysates, suggesting that the secreted galectin-1 undergoes further post-transational modifications before or after secretion [49]. It was demonstrated that extracellular 15 kDa galectin-1 is able to bind to cell surface at specific locations. Since galectin-1 lacks the required signal peptide for secretion pathways, authors suggested that post-translational modifications, resulting in the high galectin-1 molecular mass, are required for galectin-1 export to the extracellular compartment [49]. In addition, Seelemeyer et al. showed that galectin-1 secretion depended on functional interactions between the lectin and β-galactoside-containing cell surface receptors [50].

It is well documented that galectin-1 expression levels and localization depend on the biological context. In normal cells there is minimal secreted galectin-1 in the extracellular compartment [51], the majority being in the cytoplasm and nucleus [52]. In endothelial cells of normal tissues, galectin-1 is mainly localized to the nucleus and is shuttled to the extracellular space upon cell activation [53] Given its role in cell-matrix adhesion [54], it is likely that extracellular galectin-1 is required for adhesion and migration of activated endothelial cells in the extracellular matrix (ECM) [55], suggesting an important function in physiologic angiogenesis. There is extensive literature reporting significant galectin-1 upregulation in tumor cells compared to normal cells [32,49,56,57]. Moreover, it appears to be secreted at a higher level in the extracellular space of cancer cells and tumor-associated endothelial cells in several tumor types compared to normal tissue [26,53,58].

Extracellular and intracellular binding partners of galectin-1

Galectin-1 recognizes N-acetyl-lactosamine residues in several glycoproteins and glycolipids and is also involved in protein–protein interactions [21]. The lectin-carbohydrate interactions of galectin-1 occur in the extracellular compartment, whereas protein–protein interactions are intracellular [21]. Much progress was made in the last decade in identifying novel galectin-1 binding partners. Several reports argue that many galectin-1 roles related to tumor progression require interaction with these binding partners (Table 1).

Extracellular binding partners

Galectin-1 binds in a dose- and β-galactoside-dependent manner to a wide array of glycoproteins and glycolipids on the cell surface, as well as to ECM components such as laminin, fibronectin, thrombospondin, vitronectin, and osteospondin [59,60]. The bivalent binding activity of galectin-1 homodimers enables them to act as biological cross-linkers for ECM proteins and cell surface receptors. There is evidence that the pro- or anti-adhesive functions of galectin-1 occur via the enhancement or inhibition of cell-ECM interactions, respectively [61,62]. These "dual" effects may be associated with a competitive interaction of critical ECM components/cell surface proteins with galectin-1, and the co-expression of other galectin members with biologically opposite effects. It is worth noting that the presence of soluble or immobilized galectin-1 in the intracellular space can be crucial for the final outcome in galectin-1-related cell adhesion and invasion [55].

Several reports suggest that galectin-1 has a role in both homo- and heterotypic aggregation of tumor cells. In melanoma cells, galectin-1 mediates homotypic cell aggregation, at least in part, in a carbohydrate-binding dependent manner with the glycoprotein 90 K/Mac-2BP [63]. On the other hand, accumulation of galectin-1 was described in the adhesion contact points of breast cancer cells with adjacent endothelial cells [64]. Ito et al. observed that in colon cancer cells, galectin-1 interacted with the adhesion molecules CD44 or CD326, known as breast and colon cancer stem cell markers [65]. Since these surface proteins are involved in extravasation of metastatic cells by promoting cancer cell attachment to the endothelium [66,67], galectin-1 interaction with them may promote metastatic development [65].

Several cell surface glycoproteins such as integrins [68,69], ganglioside monosialic acid GM1 [70,71], CD146 [72], and neuropilin-1 (NRP1) [35] have also been identified as galectin-1 binding partners, the interaction conveying regulatory signaling to the tar-