Galectin-3 as a Potential Target to Prevent Cancer Metastasis

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ABSTRACT: Interactions between two cells or between cell and extracellular matrix mediated by protein–carbohydrate interactions play pivotal roles in modulating various biological processes such as growth regulation, immune function, cancer metastasis, and apoptosis. Galectin-3, a member of the β-galactoside-binding lectin family, is involved in fibrosis as well as cancer progression and metastasis, but the detailed mechanisms of its functions remain elusive. This review discusses its structure, carbohydrate-binding properties, and involvement in various aspects of tumorigenesis and some potential carbohydrate ligands that are currently investigated to block galectin-3 activity.

KEYWORDS: galectin-3, angiogenesis, apoptosis, tumorigenesis, TF disaccharide

CITATION: Ahmed and AlSadek. Galectin-3 as a Potential Target to Prevent Cancer Metastasis. *Clinical Medicine Insights: Oncology* 2015:9 113–121 doi: 10.4137/CMO.S29462.

TYPE: Review

RECEIVED: August 19, 2015. **RESUBMITTED:** September 27, 2015. **ACCEPTED FOR PUBLICATION:** September 30, 2015.

ACADEMIC EDITOR: William C. S. Cho, Editor in Chief

PEER REVIEW: Three peer reviewers contributed to the peer review report. Reviewers' reports totaled 711 words, excluding any confidential comments to the academic editor.

FUNDING: The work carried out by us was supported by the US Army Medical Research and Materiel Command grant W81XWH-07-1-0565, the National Institute of Health grants RO3 CA133935-01 and R41 CA141970-01A2, and the Maryland Innovative Initiative, TEDCO grant to HA. The authors confirm that the funder had no influence over the study design, content of the article, or selection of this journal.

COMPETING INTERESTS: GlycoMantra's products, particularly galectin-3 antagonists, are related to the topic of this review. HA is the lead inventor of a patent (#9,180,175) entitled "Methods of use for a natural Thomsen-Friedenreich disaccharide compound" filed by the University of Maryland, Baltimore.

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Introduction

In recent years, protein–carbohydrate interactions have been considered as very important for the modulation of cell–cell and cell–extracellular matrix (ECM) interactions, which, in turn, mediate various biological processes such as cell activation, growth regulation, cancer metastasis, and apoptosis. Thus, the identification and expression of carbohydrate-binding proteins (lectins) and their partners (carbohydrate ligands) and the detailed understanding of the molecular mechanisms and downstream effects of these protein–carbohydrate interactions are subjects of current intense research. Galectins, a family of at least 15 β-galactoside-binding proteins, are involved in growth development as well as cancer progression and metastasis.[1–5] However, the detailed mechanisms of these functions remain elusive. Based on their subunit structures, galectins are classified into three types: proto, chimera, and tandem repeat (Fig. 1).[5] Prototype galectins contain one carbohydrate-recognition domain (CRD) per subunit. Galectins-1, -2, -5, -7, -10, -11, -13, -14, and -15 are examples of prototype galectins, of which galectins-1, -2, and -7 are dimers. Tandem repeat-type galectins (eg, galectins-4, -6, -8, -9, and -12) contain two CRDs joined by a linker peptide. Galectin-3 is the only representative of the chimera-type galectin, which has one CRD at the C-terminal end. Galectin-3 is one of the most studied member of the galectin family.[2,6–9] As a multifunctional protein with increased or decreased expression in many types of human cancers, CRD-dependent or CRD-independent functions, and also its cellular locations (cell surface, nucleus, cytoplasm, mitochondria, and endosomal compartment),[10] galectin-3 has generated significant interest in cancer research over the past decades. This review describes its structure, carbohydrate-binding properties, transcriptional regulation, and its involvement in various aspects of tumorigenesis. Some potential carbohydrate ligands that are currently investigated to block galectin-3 function are also discussed.

Structure of Galectin-3

Primary structure. Galectin-3 (previously known as Mac-2, L-29, L-31, L-34, immunoglobulin E-binding protein, CBP35, and CBP30) contains three structurally distinct domains: a highly conserved 12-amino acid short N-terminal domain (ND),[7] proline- and glycine-rich long ND, and a C-terminal CRD (Fig. 2).[11] Galectin-3 is a monomer but can form multimer at certain circumstances such as at high concentration.[12] The short ND may have roles in secretion and apoptosis. Deletion of short ND blocks secretion of galectin-3,[8] while mutation of the conserved Ser6 affects galectin-3 antiapoptotic signaling activity.[13] The long ND is responsible for multimerization of galectin-3 and shows

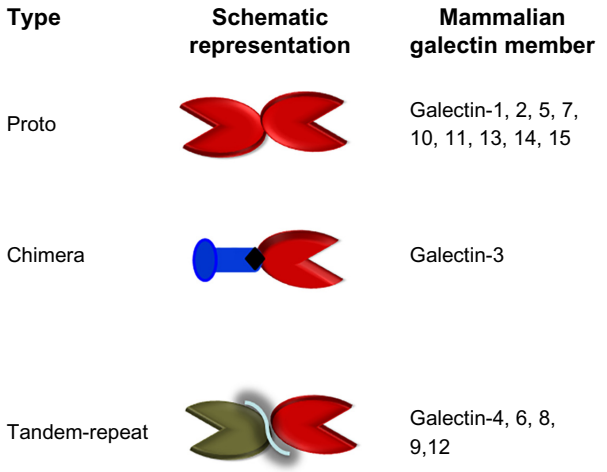

Figure 1. Classification of galectins. Schematic representation of proto-, chimera-, and tandem repeat-type galectins. They are numbered according to the order of their discovery.

positive cooperativity in carbohydrate binding.[12] This has been asserted from the observation that matrix metalloproteinases, MMP-2 and MMP-9, cleave galectin-3 at the position Ala62–Tyr63, resulting in 22 kDa fragment, which fails to self-associate.[14] The C-terminal domain of galectin-3 is composed of about 130 amino acids. It forms a globular structure like other galectins[7] and accommodates whole carbohydrate-binding site responsible for lectin activity.[15,16] Within the CRD, particularly interesting amino acid sequence is NWGR. This motif is highly conserved within the BH1 domain of the Bcl-2 family proteins and is responsible for the antiapoptotic activity of both Bcl-2 and galectin–3.[17] The NWGR motif is also involved in the self-association of galectin-3 molecules through the CRDs in the absence of saccharide ligands.[18]

Genomic and complementary DNA structures. The human galectin-3 gene (*LGALS3*) is located on locus q21–q22 of chromosome 14[19] and is about 17 kb long containing six exons and five introns (Fig. 2).[20] Exon 1 contains the major part of the 5′ untranslated sequence of messenger RNA (mRNA), while exon 2 houses the remaining part of the 5′ untranslated region, the translation initiation site and codon sequence for the first six amino acids, including the initial methionine. Exon 3 comprises long ND, while exons 4–6 house the CRD. Size of human galectin-3 mRNA (transcript variant 1) is 1017 bp – of which the open reading frame consists of 753 bp (NM_002306.3). Production of alternative transcripts arising from an internal promoter in the intron II is known in peripheral blood leukocytes.[21,22] These transcripts arise from an internal gene embedded within *LGALS3*, named *galig* (galectin-3

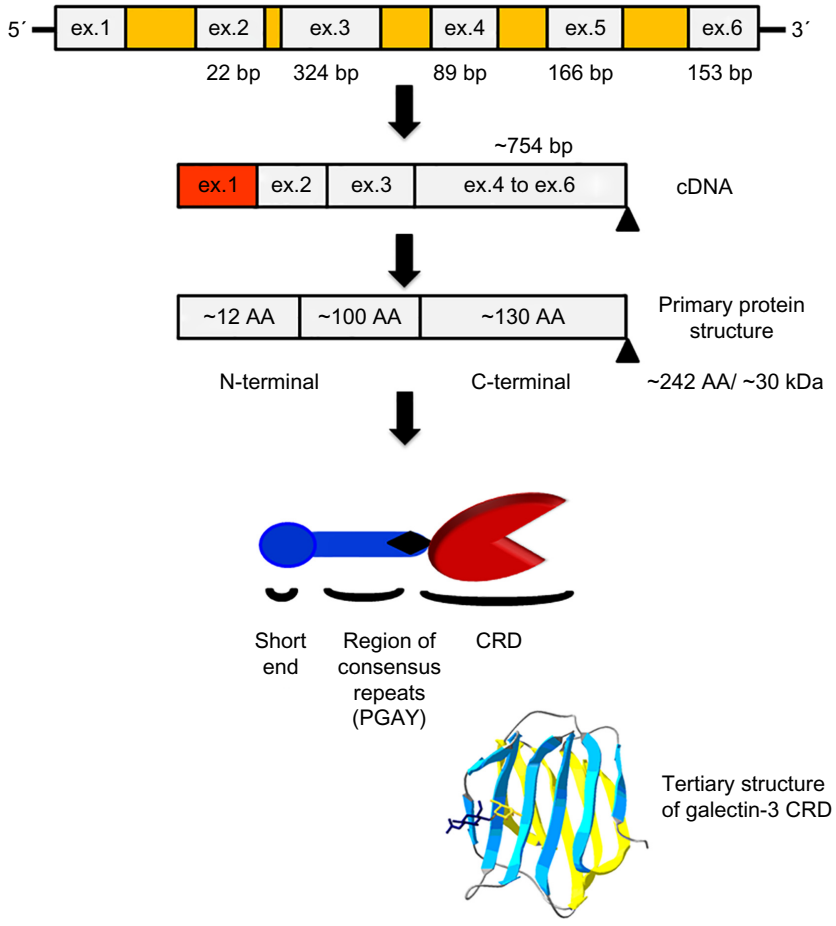

Figure 2. Structure of galectin-3. Schematic representation of nucleotide (genomic and cDNA) and protein (primary and tertiary) structures.

internal gene).[22] Galig's CRD is incapable of binding carbohydrates as it contains two overlapping open reading frames out of frame within the lectin coding sequence. However, the galig protein promotes cytochrome c release upon direct interaction with the mitochondria.[23]

Three-dimensional structure. Galectin-3 CRD was crystallized in complex with Thomsen–Friedenreich (TF) antigen (Galβ1-3GalNAcα1-*O*-Ser/Thr), lactose, TF *p*-nitrophenyl (TFN), or GM1.[24–26] The general folds of galectin-3 CRD in these complexes show a high similarity to the previously reported structures.[24] The CRD adopts a typical galectin fold in which six-stranded (S1–S6) and five-stranded (F1–F5) antiparallel β-sheets jointly formed a β-sandwich structure. The S1–S6 β-strands constitute a concave surface on which TF antigen and other glycans are bound. All these structural features are like those previously reported.[24–26] In the present structures, the residues involved in TF binding are located on S4–S6 β-strands and the loop connecting S4 and S5. Electron density maps show that TF antigen, TFN, and GM1 in the complexes are all well-ordered, and carbohydrate rings of TFs are in the chair conformations.

Carbohydrate-Binding Properties of Galectin-3 and its Ligands

Although all galectins bind β-galactoside, their ability to discriminate among carbohydrate structures is striking. For most galectins, *N*-acetyllactosamine (Galβ1, 4GlcNAc) is 5–10 times more active than lactose,[27–31] and so *N*-glycans are good ligands. Interestingly, a striking difference was observed between interactions of galectin-1 and -3 toward the TF disaccharide (TFD, Galβ1, 3GalNAc) found in *O*-glycans.[26–29] On isothermal titration calorimetry assays, galectin-3 was found to interact with TF antigen with 100-fold higher affinity compared to galectin-1.[26] The basis for the variable binding profiles of these galectins has been explained by their three-dimensional (3D) structures.[26,32,33] Although galectins lack a typical secretory signal peptide,[34] they are present not only in the cytosol but also in the ECM.[35,36] In the extracellular space, galectins bind to β-galactoside-containing glycoproteins of ECM and cell surface. Extracellular galectin-3 binds laminin,[37,38] fibronectin,[39] CD29,[40] CD66,[41] α1β1 integrin,[39] and Mac-2-binding protein.[42] Intracellularly, galectin-3 binds gemin 4,[17] Bcl-2,[43] nucling,[44] synexin,[45] and β-catenin[46,47] via protein–carbohydrate or protein–protein interactions.

Transcriptional Regulation

Although a large body of data about galectin-3 expression are available in the literature, the mechanisms of regulation of galectin-3 expression are not well understood. However, the expression of galectin-3 depends on cell type, external stimuli, and environmental conditions and involves numerous transcription factors and signaling pathways.[7] Galectin-3 expression may serve as differentiation marker for certain cell types. For example, the differentiation of the human monocytes or promyelocytic cell line HL-60 to macrophage-like cells induced by phorbol ester is accompanied by increased expression of galectin-3.[48] Galectin-3 expression is upregulated in phagocytic macrophages and thus considered as a "macrophage activation marker."[49] Galectin-3 expression is also elevated in microglia and macrophages activated by phagocytosis of myelin or when exposed to granulocyte-macrophage colony-stimulating factor.[50] In contrast, the activation of human monocytes by lipopolysaccharide and interferon-γ is accompanied by decrease of galectin-3 expression.[51] The reduced expression of galectin-3 was also observed in monocytic THP-1 cells treated with nonsteroidal[52] or corticosteroidal anti-inflammatory drugs.[53] Interestingly, galectin-3 expression is absent or barely detected in the resting lymphocytes,[54,55] but the activated B- and T-cells induce galectin-3 expression.[55] Galectin-3 could also be considered as a transformation marker since the galectin-3 expression is increased in fully *ras*-transformed fibroblasts, when cells have lost their anchorage-dependent growth.[56]

In the promoter region of the galectin-3 gene, several regulatory elements such as five putative Sp1-binding sites (GC boxes), five cAMP-dependent response element (CRE) motifs, four Adaptor Protein-1 (AP-1)- and one AP-4-like sites, two nuclear factor-kappa B (NF-κB)-like sites, one sis-inducible element (SIE), and a consensus basic helix–loop–helix core sequence are found.[19] The presence of multiple GC box motifs for binding ubiquitously expressed Sp1 transcription factor is a characteristic of constitutively expressed "housekeeping" genes. The activation of the Sp1-binding transcription factor is responsible for galectin-3 induction by Tat protein of HIV.[57] The SIE that binds sis-inducible factors was suggested to be a possible candidate for the growth-induced activation of galectin-3 gene expression, caused by the addition of serum. The presence of CRE and NF-κB-like site in the galectin-3 promoter suggests that the activation of galectin-3 expression could be regulated through the signaling pathways involving the CRE-binding protein (CREB) or the NF-κB transcription factor. The CREB/Activating transcription factor (ATF) and the NF-κB/Rel transcription factor pathways may be involved in the regulation of galectin-3 expression by the Tax protein during Human T-lymphotropic virus-1 (HTLV-1) infection of T-cells.[58] The involvement of the NF-κB transcription factor in the regulation of galetin-3 expression, as well as the Jun protein, a component of AP-1 transcription factor has recently been confirmed.[59] The regulation of galectin-3 expression through the NF-κB transcription factor was shown to be mediated by nucling, a novel apoptosis-associated protein, which interferes with NF-κB via the nuclear translocation process of NF-κB/p65, thus inhibiting galectin-3 expression on both protein and mRNA level.[60,61] In skeletal tissues, the regulation of galectin-3 expression is mediated by the transcription factor Runx2.[6] Very recently, galectin-3 expression is found to be regulated in pituitary and prostate tumors by methylation of CpG islands in promoter

region.[62–65] Galectin-3 was shown to be highly expressed in androgen-independent PC-3 and DU-145 human prostate cancer cell lines but weakly expressed in androgen-dependent Androgen-sensitive human prostate adenocarcinoma (LNCaP) prostate cancer cells.[64] Treatment of LNCaP cells with azacytidine (DNA methyltransferase inhibitor) showed restored expression of galectin-3, indicating that the promoter methylation is responsible for galectin-3 gene silencing.[64] We have also demonstrated DNA methylation on the galectin-3 promoter in LNCaP cells following polymerase chain reaction (PCR) amplification of the bisulfate-treated DNA and cloning and sequencing of the PCR product.[62]

Role of Galectin-3 in Cell–Cell and Cell–ECM Interactions

Numerous studies indicate that galectin-3 has important roles in normal development and tumorigenesis through regulating cell proliferation, apoptosis, cell adhesion, invasion, angiogenesis, and metastasis by binding to the cell surface β-galactose-containing glycoconjugates or glycolipids.[3,4,66] However, galectin-3 is also known to have CRD-independent functions intracellularly at the mitochondria.[16,67–69]

Galectin-3 expression in normal tissues: role of galectin-3 in growth development. Galectin-3 is developmentally regulated and expressed in many tissues of adults.[70,71] During mouse embryogenesis, galectin-3 first appears at the fourth day of gestation in the trophectoderm of blastocyst, followed by its expression in the notochord cells between 8.5 and 11.5 days of gestation.[70] In later stages of mouse development, galectin-3 is expressed in the cartilage, ribs, facial bones, suprabasal layer of epidermis, endodermal lining of the bladder, larynx, and esophagus.[7] In adults, galectin-3 is mainly expressed in the epithelial cells such as small intestine,[72] colon,[73] cornea,[74,75] kidney,[76] lung,[77] thymus,[78] breast,[79] and prostate.[80] The expression of galectin-3 is also detected in the ductal cells of salivary glands,[81] pancreas,[82] kidney,[83] eye,[84] and intrahepatic bile ducts.[85] Regarding cell type, galectin-3 expression is observed in fibroblasts,[86] chondrocytes and osteoblasts,[43] osteoclasts,[87] keratinocytes,[88] Schwann cells,[89] gastric mucosa,[90] endothelial cells,[91] and also immune-related cells such as neutrophils,[92] eosinophils,[93] basophils and mast cells,[94] Langerhans cells,[88,95] dendritic cells,[96] as well as monocytes[51] and macrophages from different tissues.[3,6,97,98]

Galectin-3 promotes tumor progression and metastasis: changes in cellular localization of galectin-3. Galectin-3 is expressed in many tumors and possibly plays an important role in tumor progression and metastasis.[6,7,9,43,79,80,98,99] However, the intensity of the galectin-3 expression in tumors depends on the type of tumor, its invasiveness, and metastatic potential.[44,45] For example, increased expression of galectin-3 is observed in colon, head and neck, gastric, endometrial, thyroid, liver, bladder cancers, and breast carcinomas.[46,47,79,99–101] Galectin-3-transfected human breast cancer cells BT549, which is galectin-3 null, after intrasplenic injection, formed metastatic colonies in the liver, while gal3 null BT549 cells did not.[102] Change in cellular localization of galectin-3 is also observed during progression of various cancers. For example, downregulation of galectin-3 expression has been demonstrated in colorectal cancer, with increased cytoplasmic expression of galectin-3 at more advanced stages.[44,45,103] In tongue cancer, nuclear galectin-3 is decreased, but cytoplasmic galectin-3 is increased during progression from normal to cancer.[44,45] The decreased expression of galectin-3 was also observed in prostate,[64,80,104] kidney,[105] and pituitary cancers.[63] In prostate cancer, although galectin-3 is downregulated, its nuclear exclusion and cytoplasmic localization are correlated with disease progression.[64,80,106] Phosphorylation of galectin-3 at Ser6 regulates its nuclear export.[107] Recent data by us and others indicated that decreased expression of galectin-3 in pituitary and prostate tumors is, in part, due to its galectin-3 promoter methylation.[62–65] Galectin-3 expression in gastric, liver, lung, bladder, and head and neck cancers was significantly increased compared to the normal tissues and correlated with the progression of clinical stages and metastases.[101–105]

Cytoplasmic galectin-3 inhibits apoptosis. The antiapoptotic functions of cytoplasmic galectin-3 has been consistently shown in many types of cancer cells, including breast, prostate, thyroid, bladder, colorectal, pancreatic, gastric, myeloid leukemia, neuroblastoma, and some B-cell lymphoma.[68,108–114] However, galectin-3 seems to induce apoptosis in other B-cell lymphomas.[115] For this antiapoptotic function of galectin-3, several mechanisms have been proposed (Fig. 3A).[6]

For example, galectin-3 acts as a specific binding partner for activated K-Ras, which promotes strong activation of phosphoinositide 3-kinase.[105] Galectin-3 is the only member of its family that contains the NWGR antideath domain. In particular, the NWGR motif presented at the ND of galectin-3 shows a strong homology with the groove–BH1 motif interface of the Bcl-2 protein family, which appears to be essential for its antiapoptotic functions.[67] Bcl-2 translocation to the mitochondrial membrane blocks apoptosis and cytochrome c release.[106] Cytochrome c release and nitric oxide-induced apoptosis were blocked in galectin-3-transfected BT549 human breast carcinoma cells.[107] Moreover, galectin-3 binds Bcl-2 protein *in vitro* and inhibits mitochondrial apoptotic response.[16,67] Interestingly, synexin (annexin 7) is required for galectin-3 prevention of mitochondrial damage.[45] Recently, targeting and/or co-targeting Bcl-2 and Bax was proposed as promising strategies for cancer therapy.[116–118] In this context, a combination therapy with depletion of galectin-3 and Bcl-2 inhibitor and/or Bax activator might exhibit strong synergy against metastatic cancer.

Extracellular galectin-3 secreted from tumor cells induces apoptosis of cancer-infiltrating T-cells: possible role of galectin-3 in the immune escape mechanism during tumor progression. Recent studies revealed that galectin-3 can

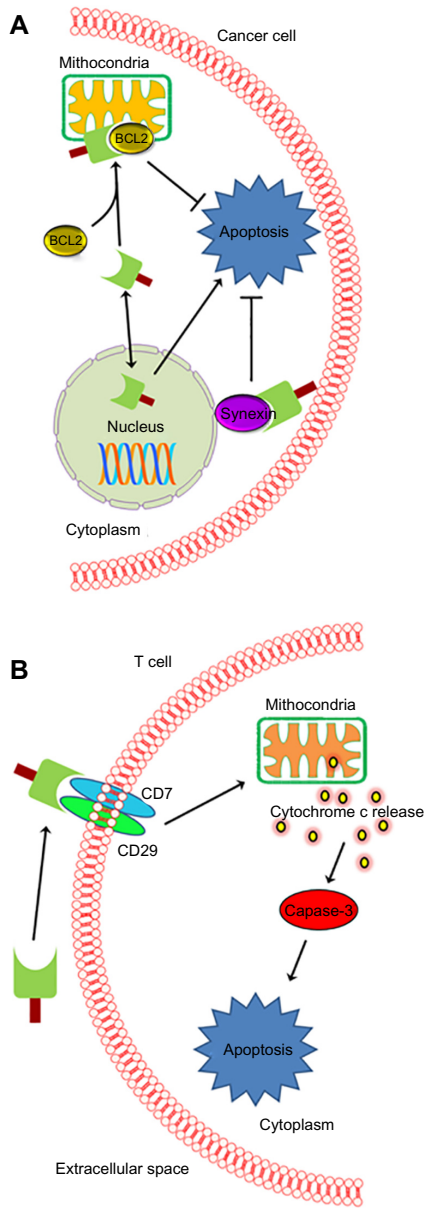

Figure 3. Function of galectin-3 in apoptosis. Schematic representation of (**A**) intracellular and (**B**) extracellular function of galectin-3. (**A**) Nuclear galectin-3 is apoptotic, while cytoplasmic galectin-3 is shown antiapoptotic. (**B**) Galectin-3 mediated apoptosis of T-cells.

induce apoptosis of activated T-cells or is responsible for deficient T-cell functions (Fig. 3B).[9,39,119] Interestingly, galectin-3-null T-cell lines, such as Jurkat, CEM, and MOLT-4 cells, were significantly more sensitive to exogenous galectin-3 than galectin-3-expressing lines SKW6.4 and H9. For example, galectin-3-transfected Jurkat cells were found more resistant to apoptosis induced by anti-Fas antibodies or staurosporine (protein kinase inhibitor) compared to the nontransfected control cells.[17,120] These differences are probably due to a balance between the antiapoptotic activity of intracellular galectin-3 and proapoptotic activity of extracellular galectin-3. Extracellular galectin-3 can also induce apoptosis in human T-cells including human peripheral blood mononuclear cells and activated mouse T-cells.[39] This would imply that tumor cells defend themselves against infiltrating T-cells by secreting galectin-3. Two major signaling pathways, one via death receptors Fas (apo-1/CD95) and the other using TRAIL (TNF-related apoptosis inducing ligand or Apo2-L), are known for extrinsic apoptotic signals.[121,122]

Cell surface glycoproteins, such as CD29, CD7, CD95, CD98, and T-cell receptor have been shown to associate with galectin-3, which may mediate induction of apoptosis by extracellular galectin-3.[68,123] For example, extracellular galetin-3 binds to the CD29/CD7 complex, which triggers the activation of an intracellular apoptotic signaling cascade followed by mitochondrial cytochrome c release and activation of caspase-3.[9]

Galectin-3 mediates homotypic and heterotypic aggregation and promotes angiogenesis, tumor cells endothelial interactions, and tumor metastasis: role of TF antigen in cancer metastasis. Several studies suggest that galectin-3 promotes tumor angiogenesis and metastasis in many cancers (Fig. 4A).[124] Disruption of galectin-3 expression could impair tumoral angiogenesis by reducing Vascular endothelial growth factor (VEGF) secretion from TGFβ1-induced macrophages.[125] Once the primary tumor is established, the formation of secondary tumors by circulating cancer cells requires embolization by aggregating with other tumor cells in microcapillaries followed by extravasation at secondary sites (Fig. 4B). In the first step of extravasation, cells bind to endothelial cells through protein–carbohydrate interactions and penetrate through the layers of endothelial cells and basement membrane. It was shown that cell surface galectin-3 mediates homotypic cell adhesion by binding to soluble complementary glycoconjugates.[126] Interactions of metastatic cancer cells with vasculatory endothelium are critical during early stages of cancer metastasis.[127] Galectin-3 mediates homotypic and heterotypic aggregation and promotes interactions between tumor cells and endothelial cells, angiogenesis, and tumor metastasis.[2,4,6] It has been shown that galectin-3 expressed in activated endothelium participates in docking of cancer cells including breast and prostate cancers on capillary endothelium by specifically interacting with cancer cells-associated TFD (Galβ1, 3GalNAc).[128–130] The TFD, present in the core I structure of mucin-type *O*-linked glycan, is generally masked by sialic acid in normal cells but is exposed or nonsialylated in malignant and premalignant epithelia.[129,130] Circulating galectin-3 has been shown to increase cancer cell homotypic aggregation by interaction with TFD on the cancer-associated transmembrane mucin protein MUC1.[131,132] Significance of galectin-3 in homotypic and heterotypic cell–cell interactions was also demonstrated by using 3D co-cultures of endothelial and epithelial cells.[79]

Many proinflammatory cytokines are overexpressed in cancer condition and are increasingly realized to play critical roles in promoting various steps in cancer progression and metastasis.[133,134] Recent studies have indicated that overexpression of galectin-3 in cancer induces secretion of several proinflammatory cytokines, hence, indirectly involved

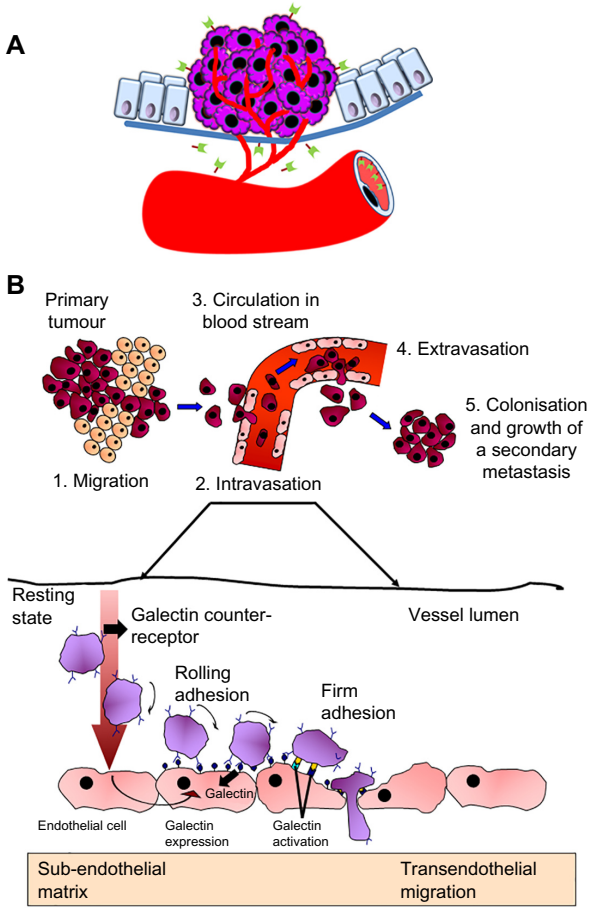

Figure 4. Function of galectin-3 in tumor angiogenesis and metastasis. (**A**) Schematic representation of galectin-3-mediated tumor cell angiogenesis. (**B**) Schematic representation of galectin-3-mediated tumor–endothelial cell interactions and tumor cell extravasation (adapted from PhD dissertation of Dr. Hannah Jane Lomax-Browne – Breast Cancer Research Group, Department of Surgery, University College, London).

in promoting metastasis.[135] Galectin-3 at pathological concentrations found in patients with metastatic colon cancer induces secretion of interleukin-6, Granulocyte-colony stimulating factor (G-CSF), soluble Intercellular Adhesion Molecule 1 (sICAM-1), and Granulocyte-macrophage colony-stimulating factor (GM-CSF) from blood vascular endothelial cells *in vitro* and in mice.[135] These cytokines interact with the vascular endothelium to increase the expressions of a number of endothelial cell surface adhesion molecules, such as E-selectin, Intercellular Adhesion Molecule 1 (ICAM-1), and Vascular cell adhesion molecule 1 (VCAM-1), resulting in increased cancer cell–endothelial adhesion and increased endothelial cell migration and tubule formation. Downregulation of galectin-3 via RNA interference decreases production of proinflammatory cytokines in monocyte-derived dendritic cells,[136] suggesting that depletion of galectin-3 could be a promising strategy for cancer therapy. Galectin-3 was also shown to stimulate capillary tube formation of human umbilical vein endothelial cells *in vitro* and angiogenesis *in vivo*, which was inhibited by specific sugars and antibodies. Overexpression of galectin-3 in galectin-3 nonexpressing prostate cancer cell line LNCaP induced *in vivo* tumor growth and angiogenesis.[112]

Galectin-3 Antagonists for Cancer Therapy

There have been a few attempts to use naturally occurring substances to control and prevent cancer metastasis. Modified citrus pectin (MCP), a pH-modified soluble β-galactosyl-containing polysaccharide obtained from the peel of citrus fruits, has been claimed to be an effective antimetastatic drug for many cancers.[137] The MCP was shown to inhibit *in vitro* tumor cell adhesion to endothelium[138] and homotypic aggregation as well as *in vivo* formation of metastatic deposits of human breast and prostate carcinoma cells in lungs and bones.[139] Another polysaccharide derived from citrus pectin, GCS-100, has been shown to have great potential to treat multiple myeloma cells, including those resistant to dexamethasone, melphalan, or doxorubicin.[140,141] It modulates myeloid leukemia cell differentiation protein-1 (MCL-1), Phorbol-12-myristate-13-acetate-induced protein 1 (NOXA), and cell cycle to induce myeloma cell death.[141]

Tumor cells released galectin-3 was found to bind glycosylated receptors at the surface of tumor-infiltrating lymphocytes (TIL), forming glycoprotein–galectin lattices that could reduce the motility and functionality of TILs.[142] Disruption of glycoprotein–galectin-3 lattices using anti-galectin-3 antibodies, or galectin-3 antagonists such as *N*-acetyllactosamine, GCS-100 (MCP-derived polysaccharide), or GM-CT-01 (a galactomannan from guar gum) boosted cytokine secretion by TIL (corrected impaired TIL).[142,143] As TFD is found exposed mostly on tumor cell surface (masked in normal cells) and also tumor–endothelial cell interactions required for metastasis are mediated by endothelium-associated galectin-3 and cancer cell-associated TFD, we reasoned that exogenous TFD would be more effective and specific to block galectin-3-mediated tumorigenesis. We purified TFD-containing glycopeptide from cod fish and showed that TFD compound could inhibit tumor–endothelial cell interactions and angiogenesis.[27] Moreover, the purified TFD compound also blocked T-cell apoptosis mediated by either recombinant, tumor-associated, or cancer patient serum-associated galectin-3.[27] It is important to point out that while these galectin-3 antagonists described above are able to limit activities of the extracellular galectin-3, they seem to be ineffective in targeting intracellular galectin-3. As intracellular galectin-3 can also contribute to the process of tumor progression through their CRD-dependent and CRD-independent intracellular ligands, alternative strategies to better develop galectin-3 antagonists or combination of galectin-3 antagonist and small interfering RNA are needed to target both intracellular and extracellular galectin-3.[10]

Concluding Remarks

Numerous studies have indicated that galectin-3 is involved in multiple stages of cancer progression and metastasis and may

render anticancer activities in several ways. First, the intracellular (cytoplasmic) galectin-3 is antiapoptotic providing survival advantage to cancer cells. Second, galectin-3 promotes tumor neoangiogenesis. Third, the extracellular galectin-3 is involved in homotypic aggregation. Fourth, tumor–endothelial cell interactions required for metastasis are believed to be mediated by endothelium-associated galectin-3 and cancer cell-associated TFD. Fifth, tumor cell secreted galectin-3 induces apoptosis of cancer-infiltrating T-cells possibly promoting immune escape during tumor progression. Although a large body of data were generated from *in vitro* studies and role of galectin-3 in various aspects of cancer was not unequivocally validated in relevant animal models, nonetheless, a few attempts to perturb galectin-3 function either by blocking its expression with siRNA or by inhibiting its activity with external carbohydrate ligands produced so far encouraging results in several preclinical models.

Acknowledgments

We apologize to the authors whose works are not cited due to the limited space.

Author Contributions

Conceived and designed the experiments: HA. Analyzed the data: HA. Wrote the first draft of the manuscript: HA, DMMA. Contributed to the writing of the manuscript: HA, DMMA. Agree with manuscript results and conclusions: HA, DMMA. Jointly developed the structure and arguments for the paper: HA, DMMA. Made critical revisions and approved final version: HA, DMMA. Both authors reviewed and approved of the final manuscript.

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