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Galectin-3: a potential target for cancer prevention

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Abstract

Protein-carbohydrate interactions play significant role in modulating cell-cell and cell-extracellular matrix interactions, which, in turn, mediate various biological processes such as growth regulation, immune function, cancer metastasis, and apoptosis. Galectin-3, a member of the β-galactoside-binding protein family, is found multifunctional and is involved in normal growth development as well as cancer progression and metastasis, but the detailed mechanisms of its functions are not well understood. This review discusses its structure, binding properties, transcriptional regulation and roles in homotypic/heterotypic cell adhesion, angiogenesis and apoptosis.

Keywords

galectin-3; angiogenesis; apoptosis; tumorigenesis; TF-disaccharide

Introduction

Interactions between cells, between cells and the extracellular matrix (ECM) are pivotal for proper cellular function. In recent years, protein-carbohydrate interactions have been considered as very important for modulation cell-cell and cell-ECM interactions, which, in turn, mediate various biological processes such as cell activation, growth regulation, cancer metastasis, and apoptosis. Thus, the identification 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 (gal), a family of 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 largely unknown. Of the fifteen members of the galectin family identified so far, gal1, 2, 5, 7, 10, 11, 13, 14, and 15 are examples of the “proto” type galectins (one carbohydrate-recognition domain [CRD] per subunit), while gal4, 6, 8, 9, and 12 are “tandem-repeat” type galectins, which contain two CRDs[6] (Fig. 1). Gal-3 is the only representative of the “chimera” galectin type and probably the most studied member of the galectin family[2, 7–10]. As a multifunctional protein with increased or

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decreased expression in many types of human cancers, it has generated significant interest in cancer research over the past decades. Here we describe its structure and roles in various aspects of tumorigenesis.

Structure of gal-3

Primary structure

Gal-3 (previously known as Mac-2, L-29, L-31, L-34, IgE binding-protein, CBP35, and CBP30) contains three structurally distinct domains: a 12-amino acid short N-terminal domain (ND), proline and glycine rich long ND, and a C-terminal CRD[11] (Fig. 2). Gal-3 is a monomer, but can form multimer at certain circumstances such as at high concentration[12]. The short ND is highly conserved in all mammalian gal-3[8] and may have at least two roles; its deletion blocks secretion of gal-3[9], while mutation of the conserved Ser6 affects gal-3 anti-apoptotic signaling activity[13]. The long ND is responsible for multimerization of gal-3 and shows positive cooperativity in carbohydrate binding[12]. For example, matrix metalloproteinases, MMP-2 and MMP-9 cleave gal-3 at the position Ala62Tyr63 resulting in 22 kDa fragment that fails to self associate[14]. The C-terminal domain of gal-3 is composed of about 130 amino acids that form a globular structure like other galectins[8]. It accommodates whole carbohydrate-binding site, which is 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 anti-apoptotic activity of both Bcl-2 and gal-3[17]. The NWGR motif is also involved in self-association of gal-3 molecules through the CRDs in the absence of saccharide ligands[18].

Genomic structure

The human gal-3 gene (*LGALS3*), located on chromosome 14, locus q21q22[19], is about 17 kb long and is composed of six exons and five introns[20] (see Fig. 2). Exon I contains the major part of the 5′ untranslated sequence of mRNA; while exon II encodes 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. The N-terminal domain of the gal-3 is located in exon III; while the CRD is in exon V. Interestingly, the intron II of *LGALS3* contains an internal promoter that drives production of alternative transcripts preferentially in peripheral blood leukocytes[21, 22]. These transcripts arise from an internal gene embedded within *LGALS3*, named *galig* (galectin-3 internal gene)[22]. Galig's CRD is incapable of binding carbohydrates as it contains two overlapping open-reading frames within the lectin coding sequence. However, the galig protein promotes cytochrome c release upon direct interaction with the mitochondria[23].

Carbohydrate-binding properties of gal-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[24–28] and so N-glycans are good ligands. Interestingly, the TF-disaccharide (Galβ1,3GalNAc) present in O-glycans is also a good ligand for gal-3, but not for gal1[25, 26]. The basis for the variable binding profiles of these galectins has been explained by their 3-D structures[29, 30]. Although galectins lack a typical secretory signal

peptide[31], they are present not only in the cytosol but also in the ECM[32, 33]. In the extracellular space, galectins bind to β-galactoside-containing glycoproteins of ECM and cell surface. Extracellular gal-3 binds laminin[34, 35], fibronectin[36], CD29[37], CD66[38], α1β1 integrin[36], and Mac-2 binding protein[39]. Intracellularly, gal-3 binds gemin 4[40], Bcl-2[41], nucling[42], synexin[43], and β-catenin[44, 45] via protein-carbohydrate or protein-protein interactions.

Transcriptional regulation

Although a large body of data about gal-3 expression is available in the literature, the mechanisms of regulation of gal-3 expression are not well understood. However, the expression of gal-3 depends on cell type, external stimuli and environmental conditions and involves numerous transcription factors and signaling pathways[8]. Gal-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 tomacrophage-like cells induced by phorbol ester is accompanied by increased expression of gal-3[46]. Gal-3 expression is up-regulated in phagocytic macrophages and thus considered as a “macrophage activation marker” [47]. Gal-3 expression is also elevated in microglia and macrophages activated by phagocytosis of myelin or when exposed to granulocyte-macrophage colony-stimulating factor[48]. In contrast, activation of human monocytes by lipopolysaccharide and interferon-γ is accompanied by decrease of gal-3 expression[49]. The reduced expression of gal-3 was also observed in monocytic THP-1 cells treated with non-steroidal[50] or cortico-steroidal anti-inflammatory drugs[51]. Interestingly, gal-3 expression is absent or barely detected in the resting lymphocytes[52, 53], but the activated B and T cells induce gal-3expression[53]. Gal-3 could be considered also as a transformation marker since the gal-3 expression is increased in fully *ras*-transformed fibroblasts, when cells have lost their anchorage-dependent growth[54].

In the promoter region of the gal-3 gene, several regulatory elements such as five putative Sp1 binding sites (GC boxes), five cAMP-dependent response element (CRE) motifs, four AP-1- and one AP-4-like sites, two NF-κB-like sites, one sis-inducible element (SIE) and a consensus basic helixloophelix (bHLH) core sequence are found[20]. The presenceof multiple GC box motifs for binding ubiquitous expressed Sp1 transcription factor is a characteristic of constitutively expressed “housekeeping” genes. The activation of the Sp1 binding transcription factor is responsible for gal-3 induction by Tat protein of HIV[55]. The SIE that binds sis-inducible factors was suggested to be a possible candidate for the growth-induced activation of gal-3 gene expression, caused by the addition of serum. The presence of CRE and NF-κB-like site in the gal-3 promoter suggests that the activation of gal-3 expression could be regulated through the signaling pathways involving the cAMP-response element-binding protein (CREB) or the NF-κB transcription factor. The CREB/ATF and the NF-κB/Rel transcription factors pathways may be involved in the regulation of gal-3 expression by the Tax protein during HTLV-I infection of T cells[56]. The involvement of the NF-κB transcription factorin regulation of gal-3 expression, as well as the Jun protein, a component of AP-1 transcription factor has recently been confirmed[57]. The regulation of gal-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[58, 59]. In skeletal tissues, the regulation of gal-3 expression is mediated by the transcription factor Runx2[7]. Very recently, gal-3 expression is found to be regulated in pituitary and prostate tumors by methylation of CpG islands in promoter region[60–63]. Gal-3 was shown highly expressed in androgen independent PC-3 and DU-145 cells, but weakly expressed in androgen dependent LNCaP cells[62]. Treatment of LNCaP cells with azacytidine (DNA methyltransferase inhibitor) showed restored expression of gal-3 indicating that the promoter methylation is responsible for gal-3 gene silencing[62]. We have also demonstrated DNA methylation on the gal-3 promoter in LNCaP cells following PCR amplification of the bisulfate treated DNA and cloning and sequencing of the PCR product[60].

Role of gal-3 in cell-cell and cell-ECM interactions

Gal-3 plays an important role 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. Gal-3 may exert its multiple biological roles intracellularly within the nucleus or the cytoplasm, or after its secretion, at the cell surface and/or the extracellular space, mediating interactions between cells and the extracellular matrix[3, 4, 6].

Gal-3 expression in normal tissues: Role of gal-3 in growth development

Gal-3 is developmentally regulated and expressed in many tissues of adults[64, 65]. During mouse embryogenesis, gal-3 first appears at 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[64]. In later stages of mouse development, gal-3 is expressed in the cartilage, ribs, facial bones, suprabasal layer of epidermis, endodermallining of the bladder, larynx and oesophagus[8]. In adult, gal-3 is mainly expressed in the epithelial cells such as small intestine[66], colon[67], cornea[68, 69], kidney[70], lung[71], thymus[72], breast[73], and prostate[74]. The expression of gal-3 is also detected in ductal cells of salivary glands[75], pancreas[76], kidney[77], and eye[78] and in intrahepaticbile ducts[79]. Regarding cell type, gal-3 expression is observed in fibroblasts[80], chondrocytes and osteoblasts[41], osteoclasts[81], keratinocytes[82], Schwann cells[83] and gastric mucosa[84], endothelial cells[85], and also immune related cells such as neutrophils[86], eosinophils [87], basophils and mast cells[88], Langerhans cells[82, 89], dendritic cells[90], as well as monocytes[49] and macrophages from different tissues[3, 7, 91, 92].

Gal-3 promotes tumor progression and metastasis: Changes in cellular localization of gal-3

Gal-3 is expressed in many tumors and possibly plays an important role in tumor progression and metastasis[7, 8, 10, 41, 73, 74, 92, 93]. However, theintensity of the gal-3 expression in tumors depends on the type of tumor, its invasiveness and metastatic potential[42, 43]. For example, increased expression of gal-3 is observed in colon, head and neck, gastric, endometrial, thyroid, liver, bladder cancers and breast carcinomas[44, 45, 73, 93–95]. Gal-3 transfected human breast cancer cells BT549, which is gal-3 null, after intrasplenic injection, formed metastatic colonies in the liver, while gal-3

null BT549 cells did not[96]. Change in cellular localization of gal-3 is also observed during progression of various cancers. For example, down-regulation of gal-3 expression has been demonstrated in colorectal cancer, with increased cytoplasmic expression of gal-3 at more advanced stages[42, 43, 97]. In tongue cancer, nuclear gal-3 is decreased, but cytoplasmic gal-3 is increased during progression from normal to cancer[42, 43]. The decreased expression of gal-3 was also observed in prostate[62, 74, 98], kidney[99], and pituitary cancers[61]. In PCa, although gal-3 is down-regulated, its nuclear exclusion and cytoplasmic localization are correlated with disease progression[62, 74, 100]. Phosphorylation of gal-3 at Ser6 regulates its nuclear export[101]. Recent data by us and others indicated that decreased expression of gal-3 in pituitary and prostate tumors is, in part, due to its gal-3 promoter methylation[60–63]. Gal-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[95–99].

Cytoplasmic gal-3 inhibits apoptosis

Intracellular gal-3 inhibits apoptosis by various mechanisms[7]. For example, gal-3 acts as a specific binding partner for activated K-Ras, which promotes strong activation of PI3K (phosphoinositide 3-kinase) [102]. Gal-3 is the only member of its family that contains the NWGR anti-death domain. Bcl-2 translocation to the mitochondrial membrane blocks apoptosis and cytochrome c release[103]. Cytochrome c release and nitric oxide-induced apoptosis were blocked in gal-3 transfected BT549 human breast carcinoma cells[104]. Moreover, gal-3 binds Bcl-2 protein *in vitro* and inhibits mitochondrial- apoptotic response. Interestingly, synexin (annexin 7) is required for gal-3-prevention of mitochondrial damage[105].

Extracellular gal-3 secreted from tumor cells induces apoptosis of cancer-infiltrating T-cells: Role of gal-3 in the immune escape mechanism during tumor progression

Recent studies revealed that gal-3 can induce apoptosis of activated T-cells[37, 106, 107]. Interestingly, gal-3-null T-cell lines such as Jurkat, CEM, and MOLT-4 cells were significantly more sensitive to exogenous gal-3 than gal-3-expressing lines SKW6.4 and H9. For example, gal-3 transfectedJurkat cells were found more resistant to apoptosis induced by anti-Fas antibodies or staurosporine (protein kinase inhibitor) compared to the non-transfected control cells[17, 108]. These differences are probably due to a balance between the anti-apoptotic activity of intracellular gal-3 and pro-apoptotic activity of extracellular gal-3. Extra-cellular gal-3 can also induce apoptosis in human T cells including human peripheral blood mononuclear cells (PBMCs) and activated mouse T-cells[37]. This would imply that tumor cells defend themselves against infiltrating T-cells by secreting gal-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[109, 110].

Cell surface glycoproteins such as CD29, CD7, CD95, CD98, and T-cell receptor (TCR) have been shown to associate with gal-3, which may mediate induction of apoptosis by extracellular gal-3[111–113]. For example, extracellular gal-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[106].

Gal-3 mediates homotypic and heterotypic aggregation and promotes tumor cells endothelial interactions, angiogenesis, and tumor metastasis: Role of TF antigen in cancer metastasis

The formation of secondary tumors by circulating cancer cells requires embolization by aggregating with other tumor cells in micro capillaries followed by extravasation at secondary sites. 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 gal-3 mediates homotypic cell adhesion by binding to soluble complementary glycoconjugates[114, 115]. Interactions of metastatic cancer cells with vasculatory endothelium are critical during early stages of cancer metastasis[116]. Gal-3 mediates homotypic and heterotypic aggregation and promotes interactions between tumor cells and endothelial cells, angiogenesis, and tumor metastasis[2, 4, 7]. It has been shown that gal-3 expressed in endothelium participates in docking of cancer cells including breast and prostate cancers on capillary endothelium by specifically interacting with cancer cells-associated TF-disaccharide (TFD, Galβ1,3GalNAc)[117–119]. 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 non-sialylated in malignant and premalignant epithelia[118, 119]. Circulating gal-3 has been shown to increase cancer cell homotypic aggregation by interaction with TFD on the cancer-associated transmembrane mucin protein MUC1[120, 121]. Significance of gal-3 in homotypic and heterotypic cell-cell interactions was also demonstrated by using three-dimensional co-cultures of endothelial and epithelial cells[73]. Gal-3 was shown to stimulate capillary tube formation of human umbilical vein endothelial cells (HUVEC) *in vitro* and angiogenesis *in vivo*, which was inhibited by specific sugars and antibodies. Overexpression of gal-3 in gal-3 non-expressing prostate cancer cell line LNCaP induced *in vivo* tumor growth and angiogenesis[122].

Natural carbohydrate compounds to prevent gal-3-mediated tumorigenesis

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 anti-metastatic drug for many cancers[123]. The MCP was shown to inhibit *in vitro* tumor cell adhesion to endothelium[124] and homotypic aggregation as well as *in vivo* formation of metastatic deposits of human breast and prostate carcinoma cells in lungs and bones[125].

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 gal-3 and cancer cell associated TFD, we reasoned that exogenous TFD would be more effective and specific to block gal-3-mediated tumorigenesis. We purified TFD-containing glycopeptide from cod fish and showed that TFD compound could inhibit tumor-endothelial cell interactions and angiogenesis[126]. Moreover, the purified TFD compound blocked gal-3 mediated T cell apoptosis[126].

Concluding remarks

During cancer progression and metastasis, gal-3 renders anti-cancer activities in several ways. First, the intracellular (cytoplasmic) gal-3 is anti-apoptotic. Second, gal-3 promotes angiogenesis. Third, the extracellular gal-3 is involved in homotypic aggregation. Fourth, tumor-endothelial cell interactions required for metastasis are mediated by endothelium associated gal-3 and cancer cell-associated TFD. Fifth, tumor cell secreted gal-3 induces apoptosis of cancer-infiltrating T cells, thus, to promote immune escape and tumor progression. Thus, gal-3 plays multiple crucial roles in cancer progression and metastasis and so perturbation of gal-3 function either by blocking its expression with siRNA or by inhibiting its activity with external carbohydrates such as pectin or TFD would prevent tumorigenesis.

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prevents galectin-3-mediated tumor-endothelial cell adhesion, angiogenesis, and T-cell apoptosis. Submitted.

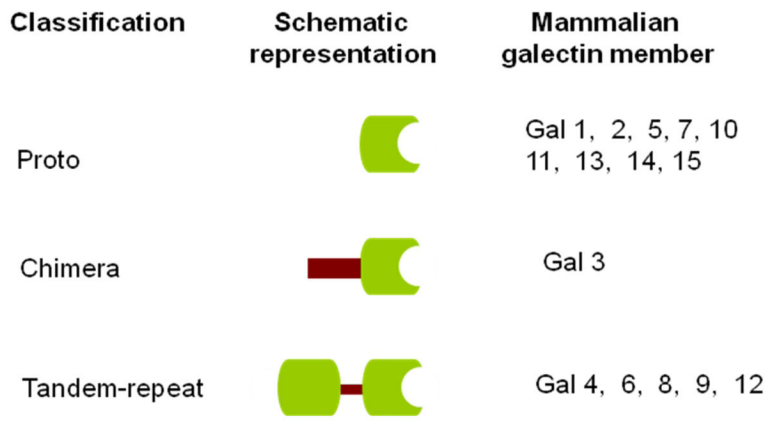

Fig 1. Classification of galectins

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

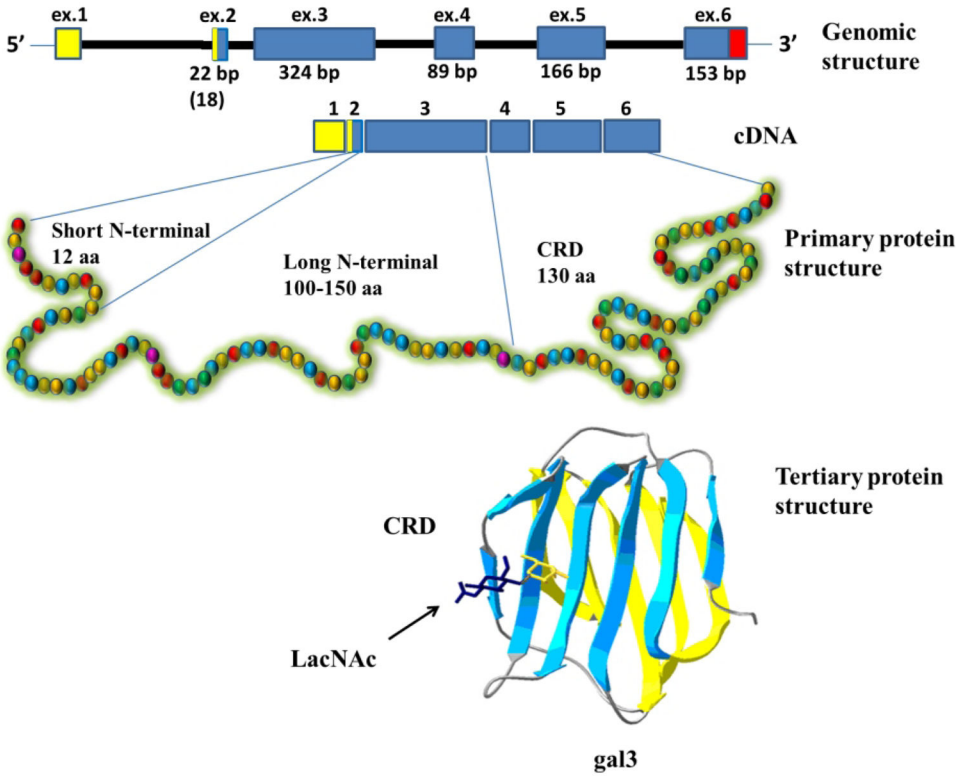

Fig 2. Structure of galectin-3

Schematic representation of nucleotide (genomic and cDNA) and protein (primary and tertiary) structures.

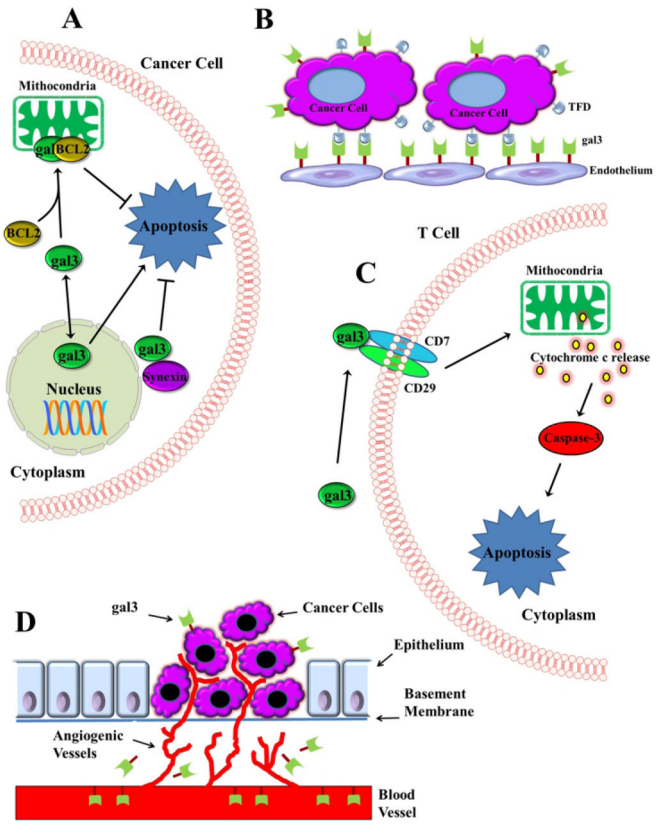

Fig 3. Function of galectin-3

Schematic representation of (A) intracellular and (B–D) extracellular function of gal-3. A. Nuclear gal-3 is apoptotic, while cytoplasmic gal-3 is shown anti-apoptotic. B. Gal-3 promotes tumor-endothelial cell interactions. C. Gal-3 promotes apoptosis of T-cells. D. Gal-3 promotes tumor cell angiogenesis.