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Galectin-1 and -3: Intracellular Pathways of Signal Transduction in Carcinogenesis (Lecture)

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ABSTRACT

The lecture was created following the analysis of experimental data and review articles presented in the PubMed database. The lecture consists of five parts summarizing the literature data on galectin-1 and -3 in terms of their modulating effect in signal transduction processes. Possible mechanisms of galectin-1 and -3 involvement in proliferation, apoptosis, angiogenesis, migration, and adhesion of tumor cells are considered. The lecture data make it possible to identify intracellular signaling molecules, whose qualitative or quantitative changes can prove the effect of candidate compounds of galectin-1 and -3 inhibitors as potential antitumor agents.

Keywords: galectin-1, galectin-3, proliferation, apoptosis, angiogenesis, migration, adhesion, carcinogenesis

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Галектин-1 и -3: внутриклеточные пути сигнальной трансдукции в канцерогенезе (лекция)

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РЕЗЮМЕ

Лекция разработана на основе анализа данных экспериментальных работ и обзорных статей, представленных в базе данных PubMed. Лекция состоит из пяти частей, обобщающих данные литературы о галектине-1 и -3 с позиции их модулирующего действия в процессах сигнальной трансдукции. Рассмотрены возможные механизмы участия галектина-1 и -3 в пролиферации, апоптозе, ангиогенезе, миграции и адгезии опухолевых клеток. Данные, представленные в лекции, позволяют обозначить внутриклеточные молекулы-посредники, качественные или количественные изменения которых способны доказать действие соединений-кандидатов ингибиторов галектинов-1 и -3 как потенциальных противоопухолевых средств.

Ключевые слова: галектин-1, галектин-3, пролиферация, апоптоз, ангиогенез, миграция, адгезия, канцерогенез

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

High toxicity of non-selective antitumor agents supports the need to develop new targeted antitumor drugs. The involvement of galectin-1 and -3 in the regulation of main stages of oncogenesis and successful results of international studies on development of inhibitory compounds make it possible to consider galectins as a potential target of new antitumor agents. The complexity of molecular mechanisms regulating tumor growth and modulating effects of galectins on various signaling pathways justify the need to identify intracellular targets. Changes in the activity of these intracellular targets will confirm the specific action of a potential inhibitory compound.

The aim of this study was to analyze and systematize data on the involvement of galectin-1 and -3 in the main stages of oncogenesis and identify potential intracellular indicators confirming the inhibitory effect of candidate compounds as potential antitumor agents.

GALECTINS AS MODULATORS OF SIGNAL TRANSDUCTION

Galectins constitute a family of β-galactoside-binding proteins with a highly conserved carbohydrate recognition domain (CRD) present in the cytosol, cell nucleus, and extracellular space [1–3]. Depending on the number and arrangement of CRD, galectins can be classified in three groups:

– prototype galectins (galectin-1, -2, -5, -7, -10, -11, -13, -14, -15) displaying one CRD capable of dimerization;

– tandem repeat-type galectins (galectin-4, -6, -8, -9, -12) displaying two homologous CRDs connected by a linker amino acid sequence;

– chimera-type galectins (galectin-3) displaying one CRD linked to a collagen-like N-terminal site and capable of oligomerization into a pentamer [2–7].

Galectins located inside cells interact with cytoplasmic and nuclear proteins (β-catenin, hnRNPA2B1, gemin4, NUP98, importin α, Alix, LAMP 1 and 2, N-CAM) through carbohydrate-independent protein – protein interactions [2, 8, 9]. Extracellularly, galectins bind to glycoconjugates on the cell surface and in the extracellular matrix (laminin, fibronectin, vitronectin, and elastin) containing the disaccharide *N*-acetyllactosamine (Galβ(1-4)GlcNAc; LacNAc) forming a galectin – glycan structure called a molecular lattice or cluster [2, 8, 10–12]. Binding of glycoproteins by galectin results in prolongation of residency time of receptors on the cell surface and, thus, modulation of strength or duration of signal transduction [2, 9, 10, 12].

One of the variants of atypical glycosylation of membrane glycoproteins characteristic of malignant cell transformation is multiple branching of *N*-glycans, that is the addition of β1,6-linked N-acetylglucosamine (β1,6-GlcNAc) to α1,6-linked mannose [12–18]. Remodeling of cell surface glycans results from genetic and epigenetic changes in enzymes regulating the glycome structure – Golgi glycosyltransferases, the best studied of which is β1,6-*N*-acetylglucosaminetransferase V (Mgat5) [19]. The presence of a large number of *N*-glycan fragments in the structure of glycoprotein receptors, such as growth factor receptors (FGFR, EGFR, VEGFR, TGF-βR, etc.) [17], cell adhesion molecules (integrin-α1β1, -α3β1, -α4β7, -α6β1, -αMβ1) [16, 20], and epithelial cell mucins (MUC1, MUC4) [2], makes them preferred ligands for binding to galectins [2, 16, 17, 20].

The capacity of galetins to bind to a large number of glycoproteins on the cell surface and in the extracellular matrix determines their biological role in aggregation [2], angiogenesis [1, 2, 8, 20], migration [1, 8], adhesion [2, 17, 18, 21], growth regulation [18, 21], apoptosis [2], and metastasis [2, 20, 21] of tumor cells.

THE ROLE OF GALECTINS-1 AND -3 IN PROLIFERATION AND APOPTOSIS

The involvement of galectins in stimulating proliferation and suppressing apoptosis of tumor cells is due to their ability to interact with the Ras proteins

and, thereby, modulate the strength and duration of signals regulating growth, proliferation, and differentiation [2, 22, 23]. In tumor cells, the H-Ras, K-Ras, and N-Ras proteins are constantly active, which promotes their continuous proliferation. The interaction between galectins-1 and -3 and activated H-Ras (H-Ras-GTP) plays an important role in stabilizing the H-Ras – GTP complex at the membrane level, which is necessary for cell proliferation and migration [3–5, 9]. Active GTP-binding forms of Ras proteins induce various effector molecules, such as Raf-1, phosphoinositide 3-kinase (PI3K), and Ral-stimulator of guanine nucleotide dissociation (Ral-GDS) (Ral-GDS) [11, 22].

Galectin-1 shifts initial and epidermal growth factor (EGF)-stimulated steady state of Ras-GTP/Ras-GDP toward Ras-GTP. The galectin-1 – Ras-GTP complex activates Raf-1 by exerting an allosteric effect on Ras-GTP and reducing the effect of Ras-GAP (GTPase activating factor, activating the GTPase protein) on GTP hydrolysis by the Ras protein [5, 22]. Galectin-1 stabilizes H-Ras and K-Ras in the GTP-bound state. The affinity of H-Ras-GTP for galectin-1 has been found to be higher than that of K-Ras-GTP, and more galectin-1 molecules bind to H-Ras than to K-Ras [22]. Galectin-3 binds mainly to K-Ras-GTP rather than to K-Ras-GDP and H-Ras. Formation of the K-Ras/galectin-3 complex enhances and prolongs EGF-stimulated activity of not only Ras-GTP and Raf-1, but also PI3-K [2, 14, 24].

The interaction of galectin-3 and the K-Ras protein results in the activation of the downstream signaling pathways PI3K/Akt, PLC/PKC, Raf/MEK/ERK, RalGDS/Ral, and TIAM1/Rac, which promotes proliferation, migration, and invasion of tumor cells [5]. The Ras inhibitor farnesylthiosalicylic acid and the mitogen-activated protein kinase/ERK inhibitor UO126 are known to suppress galectin-3-mediated resistance to apoptosis [23]. Using molecular docking methods and *in vitro* studies, it has been established that the disruption of the galectin-1/Ras interaction induced by the experimental compound LLS30 is accompanied by suppression of the Ras/ERK signaling pathway, inhibition of proliferation, and induction of apoptosis in malignant peripheral nerve sheath tumor (MPNST) [25].

C. Fischer et al. (2005) demonstrated that galectin-1 suppressed integrin-dependent growth of hepatocellular carcinoma (HepG2), breast carcinoma (T-47D), and ovarian adenocarcinoma (OV-90) cell lines following inhibition of the Ras-MEK-ERK signaling cascade and subsequent induction of transcription of the *p21* and *p27* genes. Inhibition of cyclin-dependent kinase 2 by the p27 and p21 proteins resulted in cell cycle arrest in the G_1 phase and suppression of cell growth. The authors demonstrated that the antiproliferative effect of galectin-1 required a functional interaction of galectin-1 with the α5 subunit of the integrin α5β1receptor [26]. Suppression of galectin-3 expression in prostate cancer cell line (PC-3) resulted in cell cycle arrest in the G_1 phase, elevated levels of the nuclear protein p21, and hypophosphorylation of retinoblastoma protein (pRb), providing no effect on levels of cyclins (D1 and E), cyclin-dependent kinases (CDK2 and CDK4), and the p27 protein [27].

The activation of telomerase is one of the most important stages of carcinogenesis. Galectin-1 (*LGALS1*) gene overexpression was associated with high telomerase (*hTERT*) mRNA expression in tumor cells in patients with multiple myeloma [11]. Suppression of galectin-3 expression reduced the expression of the telomerase reverse transcriptase gene *hTERT* in tumor cells in patients with gastric cancer [4].

The canonical Wnt/β-catenin signaling pathway plays a key role in regulation of cell proliferation and differentiation. In the absence of an activating signal, low concentrations of β-catenin in the nucleus and cytoplasm are maintained by a protein destruction complex that includes the proteins Axin, APC, and protein kinase GSK-3β. Within this complex, β-catenin undergoes phosphorylation and subsequent degradation. Activation of the canonical Wnt signaling pathway caused by formation of the Wnt-ligand/Frizzled receptor/LRP5/6 coreceptor ternary complex results in translocation to membrane of the Dvl, Axin, and GSK-3β proteins, degradation of the destruction complex, and suppression of β-catenin phosphorylation. Stabilized β-catenin translocates into the nucleus, binds to transcription factors of the TCF/Lef family, and activates specific target genes (c-Myc, CyclinD1, COX-2, MMP7, and ITF-2) that regulate cell proliferation, differentiation, and migration [28, 29]. Galectin-3 activates the PI3K-Akt-GSK-3β signaling cascade leading to the accumulation of β-catenin in the nucleus [30]. Suppression of galectin-3 gene expression reduces the β-catenin protein expression in serous epithelial ovarian cancer (SEOC) cells [31], expression of the β-catenin target gene *CyclinD1*, and proliferation of human pancreatic ductal adenocarcinoma tumor cells [32].

The involvement of galectin-1 in cell proliferation regulation is mediated by its interaction with the neuropilin receptor (NRP-1) [33]. Recombinant human galectin-1 has been shown to enhance proliferation and metastasis of the gastric adenocarcinoma cell line (GC AGS) by activating the NRP-1/c-JUN/Wee1 signaling pathway and to increase resistance to cisplatin [34]. Nuclear kinase Wee1 belongs to the cyclin-dependent protein kinase family and is a key regulator of the cell cycle. By binding to terminal phosphorylation sites, it inactivates cyclin B, resulting in cell cycle arrest in the G_2 phase as a response to DNA damage. The NRP-1 inhibitor EG00229 suppresses galectin-1-induced proliferation and metastasis in GC AGS cells and restores cell sensitivity to cisplatin [34].

It has been established that binding of galectin-3 to the T-antigen on the mucin MUC1 activates the MAPK and PI3K/Akt signaling pathway, which is accompanied by activation of cell proliferation and motility [35].

High levels of galectin-1 expression in HepG2 cells promote epithelial-mesenchymal transition by inducing expression of the transcription factor SNAIL1 and activating the Wnt/PI3K/AKT signaling pathway with subsequent repression of E-cadherin [21]. The SNAIL1 factor induces transcription of the *MDR1* gene causing drug resistance, and post-transcriptionally suppresses the expression of the p53 protein preventing apoptosis of multiple myeloma cells [3, 11]. In gastric cancer patients, overexpression of galectin-1 in tumor tissue is associated with elevated expression of the mutant p53 protein incapable of exhibiting anti-oncogenic properties [36].

Studies of the effects of galetin-3 on apoptosis have revealed that it exhibits both pro-apoptotic and anti-apoptotic activity. The determining factors include the cell type, stimulus nature, and localization of galetin-3 [37, 38]. Galectin-3 has been found to increase resistance of malignant human urothelial cells (J82) to TRAIL (TNF α-related apoptosis-inducing ligand)-induced apoptosis by enhancing activity of the Akt protein kinase in the PI3K/Akt signaling pathway. Activation of the PI3K/Akt signaling cascade results in the formation of phosphatidylinositol 3,4,5-triphosphate which binds to the pleckstrin homology domain of the Akt Ser/Thr kinase. Subsequent attachment of Akt to the cell membrane and its activation phosphorylate specific target proteins, such as Bad, procaspase-9, GSK-3 (Glycogen Synthase Kinase 3), transcription factor FKHRL1 (FKHR-like protein 1, which is a member of the Forkhead transcription factor family), thereby promoting cell survival and blocking apoptosis [39].

Galectin-3 is known to contain the anti-apoptotic motif Asp-Trp-Gly-Arg (NWGR), which is conserved in the homology domain of Bcl-2 and is critical for the anti-apoptotic function of galectin-3 [2, 4, 8, 23, 38, 39]. The antiapoptotic effects of Bcl-2 display by stabilizing the mitochondrial membrane potential and suppressing the release of the apoptosis-inducing protein cytochrome C from the mitochondria [39]. Suppression of galectin-3 gene expression increases caspase-3 expression and induces apoptosis in oral squamous cell carcinoma (OSCC) cells [40]. Galectin-3 is capable of suppressing apoptotic signals by binding to Fas/CD95 [4]. Expression of galectin-3 mRNA in leukemic B cells is associated with the expression of proliferation markers (Ki-67 and PCNA) and the anti-apoptotic protein Bcl-2 [38]. The involvement of galectin-3 in cell apoptosis regulation is also associated with the ability to interact with annexin VII, Ca^{2+} ions and phospholipid-binding protein that mediates translocation of galectin-3 to the perinuclear membrane of mitochondria to control membrane integrity and release of cytochrome C [2].

A pro-apoptotic action is characteristic of the phosphorylated form of galectin-3. In human breast carcinoma cells (BT549), phosphorylated galectin-3 has been found to promote TRAIL-induced apoptosis by activating the proapoptotic protein Bad with subsequent release of cytochrome C [37]. Proline-46 isomerization in the N-terminal region of galectin-3 has been shown to enhance T cell apoptosis via activation of the ROS/ERK cascade [41].

Extracellular galectin-1 is capable of triggering T lymphocyte apoptosis via both the receptor and mitochondrial pathways [25, 42]. It was established that the JNK/c-Jun/AP-1 signaling pathway plays a key role in galectin-1-induced apoptosis of Jurkat T cells. The pro-apoptotic effect of galectin-1 is associated with lower expression of the anti-apoptotic protein Bcl-2 and, conversely, with the induction of the pro-apoptotic protein Bad [43].

Tumor cell-secreted galectin-1 induces T cell apoptosis via interaction of the carbohydrate recognition domain with LacNAc-linked galactose residues in the CD45 receptor structure [25]. F.R. Zetterberg et al. (2024) demonstrated that the galectin-1 inhibitor GB1908 suppressed galectin-1-induced apoptosis in Jurkat T cells [44].

Galectin-1-induced cell death comes amid phosphatidylserine externalization, chromatin

condensation, DNA fragmentation, and membrane blebbing. It has been shown that apoptosis of Jurkat T cells induced by galectin-1 is associated with rapid translocation from mitochondria to the nucleus of apoptotic endonuclease G which is capable of selectively cleaving double DNA strands at poly-G sequences. Apoptosis of T lymphocytes occurs before the loss of mitochondrial membrane potential and is not accompanied by release of cytochrome C, AIF translocation, and caspase activation. Interestingly, intracellular galectin-3 inhibits galectin-1-induced Jurkat T cell death. Intracellular expression of galectin-3 stabilizes mitochondrial membranes, prevents galectin-1-induced loss of mitochondrial membrane potential, and degradation of the anti-apoptotic protein Bcl-2 [45].

On the contrary, *in vitro* assessment of the effect of recombinant galectin-3 on apoptosis has revealed a dose-dependent pro-apoptotic effect on Jurkat tumor cells and CD^{4+} T lymphocytes associated with an elevated number of cells with a depolarized mitochondrial membrane [46, 47].

THE ROLE OF GALECTINS-1 AND -3 IN ANGIOGENESIS

Angiogenesis is one of the stages of invasion and metastasis of tumor cells [2]. During angiogenesis, tumor cells secrete vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) [48]. A key role of VEGF in abnormal angiogenesis is due to the activation of VEGF receptor tyrosine kinases, such as EGFR1 (Flt-1), VEGFR2 (KDR/Flk-1), and VEGFR3, on endothelial cells (Flt-4) [13]. In patients with colorectal cancer, an elevated blood level of desquamated endotheliocytes correlates with a higher concentration of galectin-1, -3, and VEGF [49].

Activation of endotheliocytes by growth factors leads to higher expression of galectin-1 and protein transfer to the surface of endothelial cells [48]. Galectins-1 and -3 secreted by tumor cells stimulate abnormal angiogenesis through VEGF-dependent and VEGF-independent mechanisms. The interaction of recombinant human galectin-1 with mouse melanoma endothelial cells (B16-F10) *in vitro* promotes transmission of H-Ras signals in the Raf/mitogen-activated protein kinase/ERK cascade, which stimulates proliferation and migration [4, 48].

By recognizing complex *N*-glycans in VEGFR2 on endothelial cells, galectin-1 triggers VEGF-like signaling including phosphorylation of VEGFR2, ERK1/2, and Akt [4, 5, 11, 13]. The involvement of galectin-1 in the stimulation of glioma angiogenesis is associated with the activation of transmembrane kinase/ribonuclease of the endoplasmic reticulum, which regulates expression of the ORP150 protein (150-kda oxygen-regulated protein) [8]. The ORP150 protein accelerates intracellular transport of the VEGF protein from endoplasmic reticulum to the Golgi apparatus for subsequent secretion [50].

Galectin-1 also interacts with neuropilin-1 (NRP-1), which serves as a VEGFR co-receptor in endothelial cells and is necessary for tumor angiogenesis [5]. In vessels localized in tumors sensitive to VEGF blockers (anti-VEGF), a high level of α2-6-bound sialic acid is reported, which prevents galectin-1 binding. Tumors resistant to anti-VEGF treatment secrete elevated amounts of galectin-1. Interruption of β1-6GlcNAc branching in endothelial cells or suppression of galectin-1 expression transforms refractory tumors into anti-VEGF sensitive ones. Elimination of α2-6-bound sialic acid increases resistance to anti-VEGF treatment. Disruption of galectin-1 interaction with *N*-glycan promotes vascular remodeling, influx of immune cells, and suppression of tumor growth [13]. The involvement of galectin-3 in tumor angiogenesis is mediated by interaction of its carbohydrate-recognizing domain with *N*-glycans on VEGFR2 and integrin-αvβ3. The formation of clusters activating FAK-mediated signaling pathways regulates VEGF expression and migration of endothelial cells and leads to an increased angiogenic response to VEGF type A (VEGF-A) [2, 4, 14, 20, 51].

THE ROLE OF GALECTINS-1 AND -3 IN CELL MIGRATION

Cell motility is based on dynamic remodeling of the actin cytoskeleton and focal adhesions. When interacting with the extracellular matrix, integrin receptors cluster in the membrane plane, activate Src, and involve paxillin, talin, and vinculin in the formation of complexes that fix microfilaments. Tyrosine kinases of cytokine receptors together with integrins activate common oncogenic signaling mediators – protein kinase Cy, PI3K, Rac/Cdc42, and the adapter proteins Grb7, Grb2, and p130cas. Cells with low activity of focal adhesion kinase (FAK) are unable to move fibronectin bound to integrins along actin filaments necessary for formation of mature fibrillar adhesions [52].

It has been established that the expression of endogenous galectin-1 in human malignant astrocytoma cells (U343MG-A, U87MG, U87MG-10)

correlates with cell migration ability and invasiveness [53]. Galectin-1 acts as the main factor inducing epithelial-mesenchymal transition and metastasis by reducing the level of E-cadherin expression, activating the Hedgehog signaling pathway, transcription of NF-kB, followed by increased expression of the genes *MMP1, S100A7* and *ankyrin-3* which are responsible for invasion and migration of tumor cells [4, 54]. Lower galectin-1 expression induced by miRNA is accompanied by a decrease in the amount of integrin-β1 on membranes of human malignant erythrocytoma cells (U87, Hs683) at cell adhesion points, accumulation of integrin-β1 inside cells, and a parallel increase in the perinuclear localization of protein kinase C and vimentin, which cause integrin recirculation [8, 55].

The role of galectin-1 in tumor cell invasion is also associated with a higher level of matrix metalloproteinases (MMP-2, MMP-9) and reorganization of actin cytoskeleton by activating Cdc42, a small GTPase of the Rho family, followed by an increase in the number and length of filopodia on tumor cells [4]. I. Camby and et al. [2002] demonstrated an increase in the motility of malignant astrocytoma cells (U87, U373) under the action of recombinant galectin-1. The authors associated enhanced migration abilities of neoplastic astrocytes with changes in organization of the actin cytoskeleton and elevated expression of the small GTPase RhoA [56].

After interaction of glioblastoma cell integrin with the extracellular matrix, RhoA attracts actin. Then more stable focal adhesion complexes are formed, which connect lamellipodia to lamellae. Rho A activity decreases, Rac1 activity increases. Focal complexes either cause migration or mature, forming focal adhesions that enhance cellular adhesion and interfere with cell mobility. At the same time, the activity of Rho A increases, while that of Rac1 decreases. Thus, switching between RhoA and Rac1 activation determines the cell ability to detach and migrate, or to lock onto and attach to the extracellular matrix [57].

The involvement of galectin-3 in regulation of invasion and motility is due to weakening of contacts between cell adhesion molecules and N-glycosylated extracellular matrix proteins, such as laminin and fibronectin [4]. Galectin-3 stimulates secretion of interleukin-6 (IL-6) and colony-stimulating factors (G-CSF, GM-CSF) by endothelial cells of human lung micro vessels (HLMVECs). Cytokines promote autocrine or paracrine metastasis by enhancing expression of adhesion molecules by endothelial cells (integrin-$\alpha_v\beta_1$, E-selectin, ICAM-1, and VCAM-1) and their migration [20, 58]. Galectin-3 activates FAK and Rac1, which are involved in reorganization of the actin skeleton and formation of lamellipodia by N-glycosylation of integrin-α3β1 [20]. The experiment run by A. Lagana et al. (2006) showed that a galectin-3-induced sequential increase in the activity of FAK and PI3K attracts conformationally active integrin-α5β1 to fibrillar adhesions and increases the turnover rate of F-actin in breast carcinoma cells [52].

The heterodimeric transcription factor HIF-1 is one of the main molecules regulating the response of cells to hypoxia. The alpha subunit of HIF-1 is stable under hypoxia, while it is destroyed under normoxia. After activation and stabilization, the HIF-1 factor moves to the nucleus and induces transcription of target genes, followed by angiogenesis stimulation. It has been found that HIF-1 activation is accompanied by elevated galectin-3 expression. The interaction of the galectin-3-integrin-α3β1 complex with a structural component of microvascular pericytes, proteoglycan NG2, stimulates endothelial cell motility and morphogenesis [8].

THE ROLE OF GALECTINS-1 AND -3 IN CELL ADHESION

Galectins are described as matrix molecules that regulate cell adhesion to the extracellular matrix by interacting with the N-acetyllactosamine sequences of *N*-glycans, integrins, and mucins [2, 8, 52]. The αv integrins (αvβ3, αvβ5, αvβ6) form an abnormal cell surface repertoire due to the high affinity of their poly-N-acetyllactosamine (LacNAc) to galectin-3. On the cell surface, integrins and the galectin-3 pentamer form clusters that regulate adhesion to the extracellular matrix and migration of tumor cells [59]. The interaction of galectins with branched *N*-glycans on integrins is accompanied by renewal and maturation of fibronectin, fibrillogenesis of fibronectin, and remodeling of actin microfilaments [60]. The interaction of galectin-3 with modified β1.6 N-acetylglucosaminyltransferase V (Mgat5) *N*-glycans in the structure of α5β1-integrin promotes its activation and formation of focal contacts, thereby regulating fibrillogenesis of the extracellular matrix and migration of mammary carcinoma cells in mice [52]. Suppression of Mgat5 activity in tumor cells reduces the number of branched *N*-glycans, number of intercellular contacts, and cell migration [60].

Mucins (MUC) are highly glycosylated high-molecular-weight proteins synthesized primarily by epithelial cells. Two subfamilies of mucins are distinguished: secreted ones (MUC2, MUC5AC, MUC5B, MUC6, MUC7, MUC8, and MUC19) perform a protective function, and membrane-bound ones (MUC1, MUC3A, MUC3B, MUC4, MUC11-13, MUC15–17, MUC20, MUC21, and MUC22) are involved in cell adhesion, intercellular receptor interactions, signal transduction, and growth and proliferation of epithelial cells.

One of the most studied mucins is type 1 transmembrane mucin (MUC1), which is physiologically expressed on the apical surface of secretory epithelial cells. MUC1 is considered to be the most significant target of galectin-3 [2]. The formation of hydrogen bonds between galectin-3 and T-antigen (CD176; Thomsen-Friedenreich antigen (TF)), a structural component of MUC1 associated with the protein framework, is important for interaction of galectin-3 and MUC1 [2, 4]. In normal epithelial cells, the T-antigen undergoes glycosylation and sialylation; in tumor cells, it is expressed in an open form.

Tumor cells are also characterized by abnormal glycosylation and overexpression of the aberrant mucin MUC1 containing shortened overly sialylated O-glycans and branched *N*-glycans. The interaction between MUC1 with unmodified T-antigen and galectin-3 leads to clustering of MUC1 on the surface of tumor cells and exposure of smaller adhesion molecules, such as E-cadherin. Subsequent cell aggregation prevents anoxosis, one of the main mechanisms for removing cancer cells from the bloodstream, due to inability of cells to adhere [2]. The formation of the galectin-3-MUC4 complex is accompanied by clustering of mucin and exposure of latent adhesion molecules, in particular integrins, which promotes the attachment of tumor cells to endothelial cells [2].

CONCLUSION

By interacting with atypical N-glycans in the structure of receptors regulating proliferation, apoptosis, adhesion, angiogenesis, and metastasis, galectin-1 and -3 promote oncogenesis. The receptor-mediated maintenance of tumor-transformed cells allows galectin-1 and -3 to be positioned as targets for compounds with antitumor effects. The challenge in this approach is related to polyreceptor interaction and involvement of various signaling cascades in key processes of tumor progression. It is necessary to perform a comprehensive assessment of the function of the receptor initiating a corresponding stage of oncogenesis and the signaling messenger proteins regulated by it to make it possible to confirm or refute an inhibitory effect of a potential compound with an antitumor effect.

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