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Galectins: a potential pharmacological target

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ABSTRACT

Aim. To consider the use of galectin-1 and galectin-3 inhibitors as potential pharmacological targets in antitumor and antifibrotic therapy.

The lecture includes the analysis of experimental research and review articles presented in the PubMed database. A brief description of the structure of galectins is given. Their generally accepted classification and features of the structure of the carbohydrate recognition domain in galectin-1 and galectin-3 are presented. The main part of the lecture describes the results of research on the development of carbohydrate-based (β-galactoside derivatives or analogues) and non-carbohydrate-based (peptide-based, carboxamide derivatives) inhibitors capable of interacting with galectin-1 and galectin-3.

The results of experiments performed on animal models and tumor cell cultures demonstrate that the antitumor effect of galectin antagonists is realized through the suppression of proliferation and metastasis, activation of tumor cell apoptosis, and modulation of the antitumor immune response. Antagonists of galectin-1 and galectin-3 potentiate the effect of antitumor drugs and have an antifibrotic effect. Some of the compounds discussed in the lecture are undergoing clinical trials. The data presented in the lecture open up opportunities for the development and synthesis of new molecules of potential galectin-1 and 3 inhibitors.

Keywords: galectin-1, galectin-3, galectin inhibitors, antitumor immunity, tumor, fibrosis

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Галектины: потенциальная фармакологическая мишень

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РЕЗЮМЕ

Целью работы является рассмотрение использования ингибиторов галектина-1 и галектина-3 как потенциальных лекарственных средств противоопухолевой и антифибротической терапии.

Лекция разработана на основе анализа экспериментальных и обзорных статей, представленных в базе данных PubMed. Дана краткая характеристика строения галектинов, представлены их общепринятая классификация и особенности структурной организации углевод-распознающего домена галектина-1 и галек-

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тина-3. В основной части лекции описаны результаты исследований по разработке молекул-ингибиторов углеводной (производные или аналоги β-галактозида) и неуглеводной (на основе пептидов, производные карбоксамида) структуры, способных взаимодействовать с галектином-1 и галектином-3.

Результаты экспериментов, выполненных на лабораторных животных и культурах опухолевых клеток, демонстрируют, что противоопухолевое действие антагонистов галектинов реализуется через подавление пролиферации, метастазирования, активацию апоптоза опухолевых клеток и модуляцию противоопухолевого иммунного ответа. Антагонисты галектина-1 и галектина-3 потенцируют действие противоопухолевых лекарственных средств и оказывают антифибротический эффект. Ряд рассмотренных соединений проходит фазу клинических исследований. Представленные в лекции данные открывают возможности для разработки и синтеза новых молекул – потенциальных ингибиторов галектина-1 и галектина -3.

Ключевые слова: галектин-1, галектин-3, ингибиторы галектина, противоопухолевый иммунитет, опухоль, фиброз

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

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Studies of antitumor immunity molecular mechanisms substantiate the rationality of target approaches to cancer therapy. Galectins are one of the promising targets that support the immunosuppressive microenvironment of tumor cells [1–7]. Galectin-mediated mechanisms dysregulating immune responses that promote tumor growth and metastasis include inhibition of activation and induction of apoptosis of T lymphocytes, expansion of $Foxp3^+$ T-regulatory cells and their immunosuppressive activity, stimulation of differentiation of tolerogenic dendritic cells, suppression of natural killer pool, and polarization of macrophages towards M2 phenotype [3, 8–11].

Involvement of galectins in proliferation of fibroblasts and their high expression in lung, liver, and myocardium tissue fibrosis also allows considering galectins as targets for antifibrotic therapy [12–15]. The role of galectin-3 in fibroblast activation includes synthesis of type I collagen and a decrease in matrix metalloproteinase activity with suppression of extracellular matrix element degradation [12]. Overexpression of galectin-1 enhances angiogenesis and production of extracellular matrix elements through activation of the PI3K/Akt pathway leading to keloid tissue formation [16].

The lecture aims to consider the current state of developing galectin-1 and galectin-3 inhibitors as potential drugs for antitumor and antifibrotic therapy.

GALECTINS

Galectins, carbohydrate-binding proteins, are expressed by a wide range of cells. They have nuclear, cytoplasmic or extracellular localization and play a major role in inflammation, tumorigenesis, angiogenesis, and fibroblast differentiation. The structural component common for galectin molecules is the carbohydrate recognition domain (CRD) with a highly conserved amino acid sequence (about 135 amino acid residues), which binds β-galactosides as part of glycoprotein and glycolipid receptors. Depending on CRD number and structural organization, galectins are classified into prototype galectins which contain one CRD and can be monomers or homodimers (galectin-1, -2, -5, -7, -10, -11, -13, -14 and -15); chimeric galectins consisting of an N-terminal collagen-like domain and a C-terminal domain containing a single CRD (galectin-3); tandem-repeat galectins containing two CRDs connected by a linker peptide (galectin-4, -6, -8, -9, -12) [1, 3, 10, 17–20].

Among the galectin family, special attention should be paid to galectin-1 and galectin-3, the high expression of which is associated with fibrosis and poor prognosis in various types of cancer including colon, thyroid, pancreatic, bladder, stomach, kidney

carcinomas, squamous cell carcinoma, melanoma, lymphomas, and neuroblastoma [2, 10, 21–24].

Galectins specifically recognize the Gal-GlcNAc (LacNAc) branches of N-glycans bound to cell surface glycoproteins [19, 24]. The galectin-1 CRD preferentially recognizes galactose-β1-4-*N*-acetyl-glucosamine sequences on *N*- or *O*-linked glycans [25]. The galectin-1 CRD includes five subsites (A–E). Subsite C is highly conserved being the main recognition site for β-galactopyranoside residues. The tryptophan residue (Trp68) that establishes hydrophobic interactions between the aromatic ring and CH groups of galactose is highly important in recognizing the galactose part of molecules. Specific hydrogen bonds are formed between the hydroxyl groups of the carbohydrate ligand and amino acid residues (His44, Arg48, Asn46, Asn61, and Glu71) of subsites C and D [26, 27]. The CRD of galectin-3 consists of eight amino acids such as Arg144, His158, Asn160, Arg162, Asn174, Trp181, Glu184, and Arg186 conditioning its interaction with carbohydrates. The interaction of galectin-3 with natural disaccharide ligands (Lac/LacNAc) occurs through hydrogen bonds and van der Waals forces. Hydrogen bonds are formed between OH groups of galectin (C-4 and C-6) and Glc/GlcNAc (C-3) through His158, Asn160, Arg162, Glu184, and Asn174; van der Waals forces bond galectin and Glc/GlcNAc residues via Trp181 and Arg186 [28, 29].

The immunoregulatory activity of extra- and intracellular galectins makes it possible to develop therapeutic approaches based on eliminating effects of these molecules by altering their expression or direct blocking by specific inhibitor molecules.

GALECTIN INHIBITORS

Studies aimed at developing potential inhibitors of different galectin subtypes are focused on obtaining selective compounds with high bioavailability [17]. The main parameters of synthesized molecules conditioning their prospects are as follows: high affinity for the target galectin (values of the dissociation constant (K_d) in a low nanomolar range, the ability to compete with endogenous ligands in biologically significant concentrations), selectivity for various carbohydrate recognition domains of the target galectin, and cellular uptake and stability in biological media [30].

Most known galectin antagonists are glycomimetics and are β-galactoside derivatives or analogs that target the canonical carbohydrate binding site of galectins. These include aryl-*O*- and *S*-galactosides and lactosides, carbohydrate-based triazoles and isoxazoles, *O*-galactosylaldoximes, phenylthio-β-d-galactopyranoside analogues, *N*-acetyllactosamine thioureido derivatives, talosides, and various polyvalent sugar-based compounds [31–33]. Monoclonal antibodies, galactose-based polymers, synthetic multivalent and small ligands usually have low affinity and limited bioavailability when administered orally [17].

B.A.Salameh et al. succeeded in synthesizing a collection of stable 3-(1H-[1,2,3]-triazol-1-yl)-1-thio-galactosides containing galectin-3 inhibitors (K_d=107 μm), comparable in effect to natural disaccharide inhibitors such as lactose and N-acetyllactosamine [34]. Hydroxyl groups are known to impart polarity to thiodigalactoside molecules. Replacement or removal of any hydroxyl group not involved in interaction with galectin-3 may increase ligand affinity and oral bioavailability [35].

In a transplantable melanoma model (B16/F10 melanoma cell culture) and an orthotopic breast tumor model (breast tumor cell line 4T1), intratumoral administration of thiodigalactoside was accompanied by an increased count of $CD8^+$ T-lymphocytes infiltrating the tumor, a decreased count of $CD31^+$ endothelial cells, and proliferation of tumor cells [21, 36]. Thiodigalactosides were found to inhibit antioxidant protective effect of galectin-1 on hydrogen peroxide-induced apoptosis of endothelial cells [36].

K. Peterson et al. synthesized fluorinated derivatives of phenyltriazolylthiodigalactoside and investigated their inhibitory effect on galectin-1 and galectin-3. Symmetrically substituted phenyl-triazolylthiodigalactosides showed high affinity for galectin-3 (K_d up to 1-2 nm), asymmetric thiodigalactosides containing one triptrophenyl-triazole and one coumaryl fragments showed high affinity (K_d =7.5 nm) and 46-fold higher selectivity for galectin-3 versus galectin-1 [37].

An experiment on xenografts of a lung adenocarcinoma syngeneic model in C57/Bl/6 mice showed that oral administration of low-molecular-weight galectin-3 inhibitor GB1107 (3,4-dichlorophenyl-3-deoxy-3-[4 (3, 4, 5-trifluoro-phenyl))-1H-1, 2, 3-triazol-1-yl]-1-thio-α-D-galactopyranoside) suppressed the growth of adenocarcinoma and blocked metastatic spread.

Compound GB1107 promoted the polarization of tumor stroma macrophages towards the M1 phenotype and infiltration of tumor tissue with $CD8^+$T cells. Additional block of PD-L1 (programmed cell death ligand) with monoclonal antibodies promoted increased expression of IFNγ, granzyme B, perforin 1, and Fas ligand by cytotoxic $CD8^+$T lymphocytes and tumor cell apoptosis, assessed by increased expression of caspase 3 [22].

Using competitive NMR spectroscopy, F. Hőgye et al. assessed K_d of three symmetric derivatives of thiodigalactoside, bis-(β-D-galactopyranosyl)-sulfane modified by different aromatic substituents. According to the results obtained, bis-{3-*O*-[(naphthalene-2-yl) methyl]-β-D-galactopyranosyl}-sulfane, bis-{3-*O*-[(quinolin-2-yl)methyl]-β- D-galactopyranosyl}-sulfan and bis-(3-*O*-benzyl-β-D-galactopyranosyl)-sulfan bind to galectin-3 94, 30 and 24 times stronger than the reference compound bis-(β-D-galactopyranosyl)-sulfan. The authors highlighted the major importance of cation-π interactions in binding of aralkylthiodigalactoside derivatives to the ligand [38].

D. Vrbata et al. synthesized multivalent analogues of C-3 aryl-substituted thiodigalactoside inhibitors based on *N*-(2-hydroxypropyl) methacrylamide. Using enzyme immunoassay and bio-layer interferometry, 4 compounds were selected - with the substitution of 4-acetophenyl, 4-cyanophenyl, 4-fluorophenyl, and thiophen-3-yl, which possessed high affinity for galectin-3. Experiments on tumor cell cultures showed that the cyanophenyl-substituted glycopolymer demonstrated the greatest antiproliferative, antimigration, antiangiogenic and immunoprotective activity [6].

1,4-disubstituted triazoles were found to be high-affinity inhibitors of galectin-3. Conformational analysis of 1,4-di- and 1,4,5-trisubstituted galactose C3-triazoles showed that the triazole C5 substituent interfered with galectin proteins and, thereby, caused their lower affinity versus corresponding 1,4-disubstituted triazoles. The introduction of two 1,4-disubstituted triazole fragments into thiodigalactoside was accompanied by a lower affinity for galectin-3 [39].

Using surface plasmon resonance (SPR) technology, M.F. Marchiori et al. found that synthetic glycoconjugates of methyl 3-*O*-methyl-{[(3-phenyl)-2-propane-1-oic]-1H-1,2,3-triazol-4-yl}-α-d-galactopyranoside and methyl 3-*O*-methyl-[(6-aminohexan-2-oic)-1H-1,2,3-triazol-4-yl]-α-d β-galactopyranoside bind with high affinity (K_d=7.96 μm, K_d=4.56 μm, respectively) to galectin-3 through specific cation-π (Arg144) and ionic (Asp148) interactions. By connecting two independent CRDs of galectin-3 and creating a non-covalent cross-link between the two monomers, glycoconjugate methyl-{1-(1H-1,2,3-triazol-4-yl)-2-[2-(2-ethoxy)ethoxy]ethyl-4-*O*-(β-d-galactopyranosyl)-β-d-glucopyranoside}-4-*O*-(β-d-galactopyranosyl)-β-d-glucopyranoside achieves a submicromolar affinity for galectin-3 (K_{d1}= 0.15 μm, K_{d2}=19 μm) [28].

J. Stegmayr et al. assessed the absorption of previously synthesized galetin-3 inhibitors – a 1H-1,2,3-triazol-1-ylthiodigalactoside derivative and an α-d-galactopyranoside derivative *in vitro* on a colon adenocarcinoma cell culture (Caco-2). The authors showed that the 1H-1,2,3-triazol-1-ylthiodigalactoside derivative was only slightly absorbed by cells and likely exerted its effect in the extracellular compartment. The α-d-galactopyranoside derivative is characterized by high permeability through cell membranes [30].

Modification of glycomimetic molecules by introducing benzyl substituents into the 3-hydroxyl groups of β-d-galactopyranosyl-(1→1)-thio-β-d-galactopyranoside (TDG) made it possible to obtain compounds that inhibit binding of galectin-1 and galectin-3 on the cell surface [40].

F. Zetterberg et al. developed a relatively new class of promising drug structures of potential galectin-3 inhibitors, namely 1,3-substituted α-d-monogalactopyranosides. Higher affinity of monosaccharide molecules for the ligand was achieved through a combination of interactions of orthogonal multipolar fluoroamide, phenylarginine, sulfur-π- and halocarbonyl bonds [35]. Compound GB1490 (galectin-1: K_d=0.4 μm; galectin-3: K_d=2.7 μm) is a galectin-1 inhibitor obtained by replacing six-membered aryltriazolyl substituents in the α-d-thiogalactoside molecule. It prevents galectin-1-induced apoptosis of Jurkat cells and it demonstrated high bioavailability ($F\%$ > 99%) in experiments on mice when taken orally [41].

Doubly 3-*O*-coumarylmethyl-substituted thiodigalactosides demonstrated high affinity for galectin-3 in a mouse model of bleomycin-induced

pulmonary fibrosis [42]. Thiodigalactosides GB0139 and GB1211 obtained from disubstituted monogalactosides and having a high affinity for galectin-3, reduce the expression of profibrotic genes in liver myofibroblasts and exhibit antifibrotic activity in a model of carbon tetrachloride-induced liver fibrosis and bleomycin-induced lung fibrosis in C57BL/6 mice. Thiodigalactoside GB0139 (NCT03832946) is currently in phase IIb clinical trials for the treatment of idiopathic pulmonary fibrosis for inhaled use. Compound GB1211 (5-bromopyridin-3-yl-3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2,3-triazol-1-yl]-1-thio-α-d-galactopyranoside) is undergoing phase IIa clinical trials as a potential drug for the treatment of liver cirrhosis (NCT03809052) and cancer (NCT05240131) [17].

M. Filipová et al. synthesized multivalent glycopolymer inhibitors of extra- and intracellular galectin-3 by combining poly-LacNAc-derived oligosaccharides (Galβ4GlcNAc) with copolymers of N-(2-hydroxypropyl) methacrylamide. Authors demonstrated that the synthesized glycopolymers significantly suppressed galectin-3-induced apoptosis of T-lymphocytes and migration of tumor cells in melanoma, colon, breast and prostate cancer [43].

Multivalent glycan ligands synthesized from β-cyclodextrin demonstrated a 153-fold higher affinity for galectin-3 versus monomeric glycan ligand. Maximum affinity for galectin-3 was found for the heptavalent ligand containing GalNAc (Tn antigen). Synthetic multivalent ligands based on β-cyclodextrin were shown to inhibit the binding of galectin-3 to human airway epithelial cells [44].

A typical disaccharide ligand of galectins is *N*-acetyllactosamine (LacNAc, Galβ4GlcNAc). A structure-affinity relationship study based on enzyme-linked immunosorbent assay of a series of fifteen *N*-(2-hydroxypropyl) methacrylamide-based glycopolymers with varying numbers of LacNAcs showed that the architecture and type of presentation of LacNAc (individual or clustered on di- or trivalent linkers) provided 300-fold increase in avidity for galctin-1 versus galectin-3 [45].

M. Raics et al. studied binding of two selenium-containing galectin-3 inhibitors such as di(β-D-galactopyranosyl) selenide in which two galactose rings are linked by one selenium atom, and di(β-D-galactopyranosyl) diselenide with a diselenic bond between two sugar units. Using NMR spectroscopy and fluorescence anisotropy titration, the studied compounds were found to bind to canonical S-shaped site of galectin-3. Di(β-D-galactopyranosyl) selenide demonstrated a stronger affinity for galectin-3 than di(β-D-galactopyranosyl) diselenide, but lower than thiodigalactoside which is the known inhibitor of galectin-3 [46].

Galectin inhibitors were found to be able to potentiate the effect of antitumor drugs. Thus, galectin-3 inhibitor of GCS-100 (NCT01843790) induces p53-mediated apoptosis of acute myeloid leukemia cells (myeloma cell lines U266 and RPMI8226) and enhances the effect of BH3-mimetics (drugs that inhibit anti-apoptotic proteins of the Bcl-2 and Mcl-1 family promoting the survival and chemoresistance of tumor cells [47]. Inhibition of galectin-3 by the antagonist GCS-100 increases apoptosis of prostate adenocarcinoma cell line (PC3) induced by cisplatin [48]. In a mixed culture of acute lymphoblastic leukemia (BCP-ALL) cells and bone marrow stromal cells (OP9), galectin-1 and galectin-3 inhibitors GM-CT-01 and GR-MD-02 increase sensitivity of tumor cells to vincristine and nilotinib, which was assessed by inhibition of proliferation and a lower number of viable cells [24].

One of the promising inhibitors of galectin-3 is a compound obtained from natural carbohydrate polymers that is the complex polysaccharide of belapectin (GR-MD-02). In a transplantable model of sarcoma (MCA-205 cells), prostate adenocarcinoma (TRAMP-C1 cells) and breast carcinoma (4T1 cells) in C57BL/6 and BALB/c mice, it was established that belapectin in combination with aOX40 (monoclonal antibody against OX40 (CD134)) reduces the content of myeloid derived suppressor cells (M-MDSC) in tumor tissue, proliferation of regulatory $Foxp3^+$ $CD4^+$ T lymphocytes and increases the density of effector $CD8^+$ T cells more effectively than with aOX40 monotherapy, which is accompanied by suppression of tumor growth and increased survival of experimental animals [49]. In phase I of the clinical trial, it was found that intravenous belapectin in combination with pembrolizumab (anti-PD-1 mAb) in patients with metastatic melanoma and squamous cell carcinoma of the head and neck leads to elevation of proliferating activated effector memory $CCR7^-$ $CD45RA^-CD4^+$ T cells and lower blood levels of monocytic myeloid suppressor cells [50].

An alternative to carbohydrate-based galectin antagonists are non-carbohydrate inhibitor molecules such as heterocyclic compounds, peptide-based inhibitors and peptidomimetics (OTX008/PTX008 and Anginex (β-pep25)) [33]. PTX008, allosteric inhibitor of galectin-1, suppresses aggregation, adhesion, and migration of acute lymphoblastic leukemia cells (early B-cell precursor ALL, BP-ALL) and increases their sensitivity to vincristine [51]. OTX008 (PTX008), galectin-1 inhibitor, suppresses the growth and increases oxygenation of tumor cells of human squamous cell carcinoma of the larynx (SQ20B) in an experimental mouse model (Athymic Nude, *Nu/Nu*) [31], enhances inhibitory effect of sorafenib on proliferation of hepatocellular carcinoma cells (MHCC97L) [52]. In combination with the chemotherapeutic agent of irofulven, PTX008 causes regression of ovarian tumor growth experimentally induced in mice (athymic nude, *Nu/Nu*) by introducing a human epithelial ovarian carcinoma cell line (MA148) [32].

Recently, new non-carbohydrate compounds binding C-terminal domains of galectin-3 and galectin-8C have been proposed. They are derivatives of *N*-arylsulfonyl-5-aryloxy-indole-2-carboxamide which are Cpd53 (galectin-3: K_d=4.12 μm, galectin-8C: K_d=6.04 μm) and Cpd57 (galectin-3: K_d=12.8 μm, galectin-8C: K_d=2.06 μm) compounds. Using molecular docking, the amino acids Arg144 of galectin-3 and Ser213 of galectin-8C were found to contribute to increased selectivity [5].

CONCLUSION

Galectin involvement in tumor cell transformation, metastasis, stimulation of angiogenesis and suppression of antitumor immune responses allows considering these carbohydrate-binding proteins as multifunctional targets for cancer therapy. Results of numerous studies assessing the effect of molecules with different structures on galectin-mediated effect indicate prospects of research in development of selective antagonists of galectin family individual members, and rationality of their combined use with antitumor drugs in order to enhance the chemotherapeutic effect. The high risk of tissue fibrosis of various localizations associated with increased expression of galectin-1 and galectin-3 indicates potential modulating effect on fibroblast proliferation by eliminating the effect of galectins using antagonists.

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