REVIEW ARTICLE

Emerging Role of Galectins as Molecular Targets for Cancer Therapy: A Review

Mohammad Anjum Shaik, Hong- Wai Tham

Faculty of Pharmacy, SEGI University, 9 Jalan Teknologi, Taman Sains Selangor, PJU 5, Kota Damansara, 47810, Petaling Jaya, Selangor, Malaysia

ABSTRACT

In recent decades cancer incidences and mortality rates have increased. Although there is significant progress in identifying the root causes and emerging therapies, there are many molecular, cellular mechanism's unrevealed and current treatments have yet to deliver on their promises. Common characteristics of cancer that are controlled by various mechanisms, including those involving glycosylation-dependent proliferative signalling, the ability of tumor cells and their microenvironment to sustain proliferative signalling, enhancing the replicative immortality, evading the effects of growth suppressors, resisting apoptosis, sustaining invasion and metastasis, stimulation of angiogenesis and triggering immune response are few to name. An evolutionarily conserved family of glycan-binding proteins known as galectins has a significant impact in controlling these cascades. Galectins belong to animal lectin family that function by interacting with matrix glyco-proteins on extracellular surface and also with nuclear proteins modulating the cell signalling cascades intracellularly. In this review, we analyse how galectins influence the cellular pathways that control tumor activity, providing relevant examples and highlighting their therapeutic perspective in the fight against cancer.
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Corresponding Author:
Tham Hong Wai, PhD
Email: thamhongwai@segi.edu.my
Tel: +603 6145 1777 (ext. 3191)

INTRODUCTION

Cancer is a complicated illness that involves a series of gene-environment interactions in a sequential process that cannot develop unless many events like DNA repair, apoptotic and immunological activities are dysfunctional (1). The global burden of cancer continues to rise, owing largely to the aging and growth of the world population, as well as a number of contributing factors such as specific genetic background, chronic exposure to various environmental stresses, biological factors and poor diet (2). All of these risk factors contribute to the accumulation of genetic alterations or mutations in several essential proteins in cells, which helps to initiate carcinogenesis. Evaluating the possible impact of discovered genes, gene products and their regulation is the key objective in cancer research. Recent research advances indicates that glycans, particularly oligosaccharide chains, may have a role in carcinogenesis as galectin recognition patterns (3).

Lectins aid in recognition of the carbohydrates bound to proteins and lipid molecules referred as glycoconjugates over the cell external surfaces(4). They have Carbohydrate recognition domains (CRDs) that bind to beta galactoside having glycans. These CRDs are conserved units with 130 amino acids(5). On a structural basis they are classified into (1) galectins containing one CRD which can form homodimers. The group of galectins- galectin-1, 2, 5, 7, 10, 11, 13, 14, and 15 fall under this subgroup. (2) The galectins with two domains of carbohydrate recognition sequences with a linker. This subgroup includes galectin-4 6, 8, 9, 12 (3) chimeric galectins with N-terminal extensions forming oligomers like galectin-5, 6, 11, 15 which are not observed in human beings(6).

Galectins do not have a particular signal sequence, which is usually very important for protein production via the classic secretory pathway. Nevertheless, some galectins can be released by the cell, most likely via a non-classical secretory pathway, and can be identified in the extracellular space(7). The expression of galectins is proper balanced during the time of cell differentiation and development of the tissues. The expression can be modulated due to physiological and anatomical conditions (Chiariotti et al., 2002).

Galectins are easily dispersed throughout a cell, including the plasma lemma, cytoplasm, and nucleus(8).

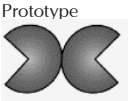
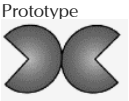
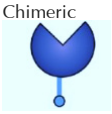
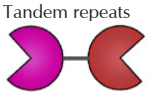
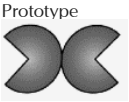
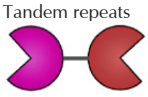
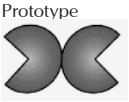
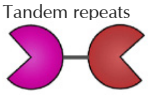
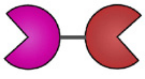
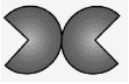
According to recent research, galectins are frequently overexpressed in malignant cells, especially in cells that do not usually express the specific galectins. Brief summary of the distribution and regulation in various cancers is represented in Table I. A normal cell expresses a few distinct galectins, but if the normal cell develops into a neoplastic cell, these galectins gets down regulated (9).This increased galectin expression correlates with tumour aggressiveness and the development of the metastatic phenotype in many cases, showing that galectins may affect tumorigenesis and influence the severity of the disease as represented in Figure 1 (10).

As a result of these findings, galectins may play a significant function in cancer biology. In this review, we emphasize on galectin effects in tumour progression, apoptosis, angiogenesis, metastasis and galectin antagonists.

ROLE OF GALECTINS IN NEOPLASTIC CELL TRANSFORMATION

Galectins can be bivalent or multivalent depending upon the number of binding regions. They are capable of interacting with the glycol-conjugates over the cell surface on membrane by forming the clusters which can lead to changes in signalling cascades(12). In the same way they are also able to provide anchorage to few oncogenic proteins so as to promote the signalling leading to cell transformation. The downstream molecules induced due to interaction between oncogenic proteins and galectins can aid in activation of transcription factors that can promote cell phenotypic changes by continuously expressing related genes (13). Evidences show that both galectins-1 and 3 are involved in such mechanisms. The phenotype characteristics of a neoplastic cell were disappeared when galectin-1

Table I: The distribution of various galectins including the regulation and subtype, gene coding &human locus data. (Adapted from (46))

Type of Galectin	Sub-type	Distribution	Regulation	Gene encoding and Human Locus
1	Prototype 	Skeletal, muscle and heart tissues	Upregulated in most of transformed cells and down regulated in head and neck cancers.	LGALS1, 22q12
2	Prototype 	Gastro Intestinal tract	-	LGALS2,22q12
3	Chimeric 	Macrophages, Epithelia	Upregulated in thyroid, CRC, Renal failure & downregulated in breast, ovarian and prostate cancers	LGALS3, 14q21-22
4	Tandem repeats 	Gastro Intestinal tract	Upregulated in Liver cancer& down-regulated in colon	LGALS4,19q13.2
5	Prototype 	Reticulocytes	-	
6	Tandem repeats 	Gastro Intestinal tract	-	-
7	Prototype 	Epithelial cells	Upregulated in Breast cancer and downregulated in bladder and skin related cancers	LGALS7, 19q13.2
8	Tandem repeats 	Kidney, Lungs, Liver, Colon	Upregulated in pancreatic and Liver cancer & downregulated in colon cancer	LGALS8, 1q42-q43
9	Tandem repeats 	Kidneys and GI Tract	Upregulated in Hodgkin's Lymphomas	LGALS9, 17q11
10	Prototype 	Basophils, Eosinophils	-	CLC

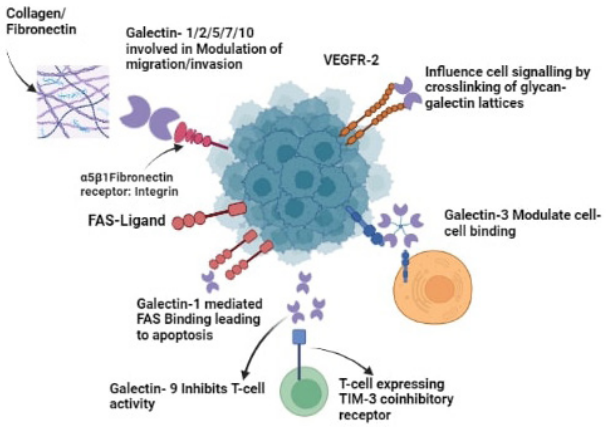


Figure 1: An illustration of the structure of galectins and their functional interactions with cell-surface and extracellular glycoconjugates is summarized w.r.t invasion of cancerous cells, galectin mediated binding, immune escape etc. (Created with BioRender.com, Modified and Adapted from Figure 1 in Ref (11))

expression was inhibited in human glioma cells (14). Galectin-1 upregulation promotes cell transformation in fibroblasts, showing that this protein is involved in the development of malignant cells (15).

Whereas in both thyroid papillary and breast carcinoma suppression of galectin-3 lead to disappearance of transformed phenotype in cell culture (16). It should also be noted that in an earlier study TAD-2 (cell line) normal thyroid follicular cells were transfected with galectin-3 cDNA still led to neoplastic transformation (17). This is why the processes and pathways through which galectin-3 play a role in cell transition into malignant cells remain a mystery.

The ability of cancer cells to sustain uncontrollable cell proliferation makes them easily distinguishable. Proliferative signaling may be affected by glycan alterations as a result of altered expression of glycan-binding proteins or transcriptional or epigenetic regulation of glycan-modifying enzymes. One of the most prevalent characteristics of human cancer is RAS gene mutation(18).The tumors generally express RAS proteins like HRAS,KRAS and NRAS with point mutations among them that are proved to have relationship with the phenotype of tumor(19). The galectin-1 acts as binding partner to HRAS thereby leading to expression of Extracellular signal regulated kinase (ERK-2)(20). Subsequently galectin-3 binds to KRAS initiating downstream signalling of PI3K-AKT pathway. Their capabilities as binding partners to HRAS and KRAS inducing ERK1/2 and AKT cascades respectively trigger these intracellular signal transduction cascades that control cell growth and proliferation, immune escape, metastasis and invasion. (21).

CONTRIBUTION OF GALECTINS IN ENHANCED METASTASIS AND INVASIVENESS

Tumor metastasis is a complex biological phenomenon that is governed by several interactions amongst neoplastic and host cells (22). The movement of the neoplastic cells starts with the formation of irregular pseudopods which help in the infiltration in basal lamina(23). The enzymatic dissolution is an important step involving the Plasminogen activators that help in formation of plasmin ,collagenases, stromelysins destructing the fibrin ,collagen, fibronectins to get separated from the matrix and access the underlying connective tissue(24). Once the initial tumor has developed, circulating cancer cells must be assembled with other tumor cells in microcapillaries, followed by extravasation at secondary sites, so as to continue with development of secondary tumors (25). Through protein-carbohydrate interactions, cells connect to endothelial cells in the initial stage of extravasation and pass through the layers of endothelial cells and basement membrane. It has been established earlier in data that cell surface galectin-3 binds to soluble complementing glycoconjugates to mediate homotypic cell adhesion which means clustering of solely cancerous cells only without non-cancerous ones. Galectin-3 enhances connections between tumor cells and endothelial cells to enable the homotypic aggregation and was reported to have role in many of the above mentioned mechanisms as represented in Figure 2 (26).

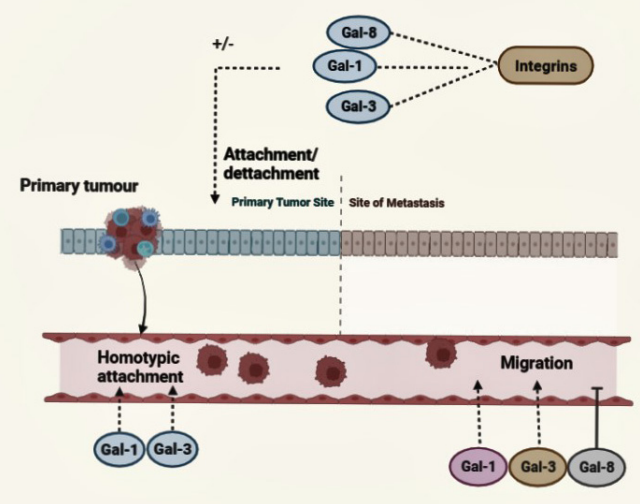


Figure 2: The spread of a tumor from its initial location to its secondary metastatic site is a multi-step process that involves cell-to-cell adhesion, detachment, cell migration, and angiogenesis. A small number of galectins interact with integrins to increase cancer cell adherence. However, the loss of intercellular adhesion is critical for cell motility. In the picture, several members of the galectin family collaborate with integrins to induce matrix dissociation, which promotes cell migration and aids in the adherence of homotypic malignant cells at the secondary site. (Created with BioRender.com, Modified and Adapted from Figure 4 in Ref (34))

Galectins have been identified to control the invasiveness and motility of cancer cells via regulating fascin-1, an actin-binding protein located along the filopodia. Cancer pathways hijack fascin-1 expression, allowing increased fascin-1 to promote motility as cell protrusions rise (27). Fascin-1 has been shown to interact with B-catenins, promoting the over expression of this actin binding protein through controlling the Wnt-cascade. Through c-jun over expression, the protease activated receptor-1 and matrix metallo protease-1 are usually upregulated in cancer. Galectins are also indirectly involved because they interact with c-jun (28). They also play a significant role in metastasis via altering PAR-1(Protease activated receptor-1) and MMP-1 (Matrix Metallo Proteases-1), according to current research (29).

Galectin-3 facilitates in modulating the tumour cell detachment from the previous location, regulating tumour cell migration. It has been demonstrated to bind to extracellular matrix glycoconjugates such as laminin and fibronectin, as well as intracellular and extra cellular elastin, and collagen IV (30).It was well documented in earlier research that loosening intercellular connectivity among the tumour cells can initiate metastasis (31). Galectins do this by attaching directly to cell adhesion molecules or by sterically obstructing the regular interactions between cell adhesion molecules that allow them to maintain cell–cell contacts. Galectin-3 interacts with glycans of matrix such as fibronectins increase invasion. On other hand, galectins due to their multivalent characteristics can hold the cells to the matrix and initiate cell adhesion. So they can suppress the detachment of cells, but importantly this process would be helpful for the heterotypic attachment of tumour cells to endothelial cells at distal regions (32). In-vitro studies using breast cancer cells showed elevated levels of galectin-3 which helped in attachment of cancerous cells to monolayer of endothelial cells. They may also govern metastasis by binding to integrins and controlling their expression (33).

GALECTINS IN APOPTOTIC REGULATION

Apoptosis can be extrinsic, involving the death receptor, or intrinsic, involving mitochondria. The death receptor is made up of a death domain that is responsible for inducing the death signal (35). The glycans linked to death receptors like as CD95 (Cluster of differentiation 95) and TRAIL-Rs (Tumor Necrosis Factor (TNF) related Apoptosis-inducing ligand-receptor) have a role in the activation or suppression of apoptotic signals. The death receptor family consists of six members: TNFR1(TNF Receptor-1), CD95, DR3 (Death receptor-3), TNF related apoptosis inducing ligand (TRAIL-R1), TRAIL-R2 and DR6. When agonistic molecules bind to CD95 or TRAIL-Rs, a DISC-death-inducing signalling complex is developed in the cell membrane.

In terms of the extrinsic route, galectin-3 binds to both CD95 and TRAIL-Rs at the extracellular domains, but the consequences induced are entirely different. Galectin-3 has been shown to crosslink with TRAIL-Rs on colorectal cancer cells, assisting in the inhibition of DISC. Galectin-3 has been discovered to form heterodimers with TRAILS-Rs in metastatic colon cancer cells, preventing DISC formation and suppressing apoptosis. However, galectins have also been shown to play a pro-apoptotic effect when interacting with CD95. One of these reported causes might be alterations in glycosylation patterns in these domains' extracellular areas. In the DR-mediated pathway, galectins have been found to exert both pro- and anti-apoptotic effects. A closer look at the glycol structure of domains like CD95 and TRAILS-Rs, as well as the structures of these regions after galectin binding, might provide further light on the subject (36).

The galectin interaction isn't just linked to DR pathways. Intracellular galectin-1 promotes apoptosis in human T-cells in a caspase-independent manner, as previously demonstrated. Upregulation of galectin-2 in activated T-cells was also connected to an increase in Bax and a decrease in Bcl-2 levels, favouring pro-apoptotic activity in another investigation.

Galectins showed anti-apoptotic properties when investigated in many cancer types like thyroid, breast, prostate, colorectal and pancreatic cancers. The galectin encoding gene when induced in cancer cells, the stimuli of apoptosis was elevated. The protein is assumed to be moving from the cytosol or the nucleus to membrane of mitochondria and change the membrane potential. According to a study by Bong Ki Moon and group, the release of cytochrome c and nitric oxide induced apoptosis were blocked in human breast carcinoma BT549 cells induced with galectin-3 (37). The genes for galectin-3 and Bcl-2 share a considerable amount of genetic similarity (48 percent protein sequence similarity). The CRD region of galectin-3, in particular, contains a four-amino-acid motif known as an Asn-Trp-Gly-Arg (NWGR), which is highly conserved in the BH-1 domain of the Bcl-2 family. The galectin-3 is only one of its family having anti-death domain NWGR. This shows homology with a groove in Bcl-2 protein, as its intervention in mitochondrial membrane causes apoptotic blockage (38).

Conversely Galectin-7 and 12 when over expressed in cancer cell lines, induced apoptosis by regulating intracellularly with some unknown mechanisms. This apoptotic role of galectins is still unrevealed (39). So the galectins can be both pro-apoptotic and majority anti-apoptotic regulating the process either at the level of surface by binding to the glycoproteins or interacting with intracellular apoptotic-related proteins. So, depending on the kind of galectin and/or galectin target protein, galectins can either activate or inhibit apoptotic signalling pathways in cancer cells.

ROLE OF GALECTINS IN INDUCING ANGIOGENESIS

One of the important steps in the process of cancer development is angiogenesis. Among the family members galectin-3 has shown effects on angiogenic activity in-vitro(40). In an experimental study on human breast cancer transplanted in immune-compromised mice also show elevated levels of galectin-3, in addition the density of capillaries also increased compared to controls (40). This substantial data supports the hypothesis that galectin-3 induces angiogenesis. Markowska and group found that galectin-3 controls vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) mediated angiogenesis. They hypothesised that galectin-3 carbohydrate binding region binds with integrin and, as a multimer, cross-links and clusters the integrin while activating FAK-mediated signalling pathways that alter endothelial cell movement in the angiogenic cascade (41).

Galectins-1, 3, 8, and 9 are abundantly expressed in the endothelial cells (EC) of tumor endothelium. They can be found in both the nucleus and the cytoplasm of EC. Endothelial galectin-1 overexpression has been found in prostate, lung, and oral malignancies (42).The inactive EC must be adjusted during the angiogenesis process, and this stage is controlled by growth factors such as EGF, VEGF, and bFGF. They execute functions successfully by interacting at the surface level, causing downstream alterations. By interacting with co-receptors, galectins have the ability to augment or prolong cascades (43).

There are many anti-angiogenic agents targeting fibroblast growth factor and vascular endothelial growth factor and also with their receptors (44). But long term use of same targets can lead to drug resistance thereby cancerous cells can tactic mechanisms to up-regulate other angiogenic factors (45).More research utilising diverse models to examine the role of galectin-3 in various stages of angiogenesis is needed to have a more comprehensive understanding of this potentially significant and intriguing field.

ANTAGONISTS OF GALECTINS

As previously stated, targeting galectins in cancer treatment is a very appealing method. Several studies are attempting to re-sensitize tumour cells to the apoptotic signalling pathways, metastasis and angiogenic pathways by focusing on galectins(47). Several natural compounds, small drug molecules have been shown to have antagonistic effect towards them. The logical design of these inhibitors is based on the notion of blocking interactions between galectins and their interacting partners(48). In general, inhibitors are classified into two classes. One category includes carbohydrate-based inhibitors, while another includes non-carbohydrate-based galectin inhibitors. Glycodendrimers and Lactose-based, Talose-based modified sugars typically come under the first category. Natural polysaccharides with galectin inhibitory properties include Pectasol-C and Davant. Heterocyclic compounds and peptide-based inhibitors are examples of the latter. DibenzoFulvene and OTX008 are highly effective Gal-1 inhibitors with antiangiogenic properties (49).

Over the last two decades, few inhibitors have been clinically studied. Among those evaluated were GCS-100, Belapectin (GR-MD-02), modified Citrus Pectin TD139, OTX008, GB-1211, and GM-CT-01 (Davant). The outcomes of some of the galectin experiments are uncertain, and a few trials were terminated (50). Table II summarizes all of the data of the investigation, the cancer targeted, and the clinical trials.

According to the data at www.clinicaltrials.gov in this study, a 3+3 Phase I design was used with dose-escalation of GR-MD-02 in combination with the standard therapeutic dose of pembrolizumab in patients with advanced melanoma who have progressed after receiving ipilimumab which is CTLA-4 Cytotoxic T-Lymphocyte antigen-4 and/or BRAF (Proto-oncogene B-Raf) targeted therapy when a BRAF mutation is present, non-small cell lung cancer patients who have progressed after receiving targeted therapy, or head and neck cancer patients(51). Enrollment in this research is suspended and the study is further delayed due to some investigations with owner.

To determine the safety and effectiveness of GB1211 (a galectin-3 inhibitor) in conjunction with atezolizumab in patients with non-small cell lung cancer, three distinct phases of the clinical trials were conducted. PART A's objective is to evaluate the safety and tolerability of GB1211 when used in conjunction with atezolizumab over the course of three weeks. In contrast, the objective of PART B is to compare the safety and tolerability of the drug GB1211 in combination with atezolizumab to those of atezolizumab and a placebo over the course of 12 weeks. The adverse event frequency and severity were to be reported. The purpose of Part C is to examine the long-term safety and tolerability of GB1211 with atezolizumab in comparison to atezolizumab alone during a time period of 12 to 40 weeks (52).

Whereas Galectin-1 inhibitor OTX008 is a calixarene-based substance that is delivered subcutaneously (53). It is widely known that certain cancer types overexpress the galectin-1 protein, which is associated with poor prognosis and accelerated metastasis growth. Pre-clinical in vitro and in vivo research revealed that OTX008 reduces galectin-1 expression. In various animal cancer models, OTX008 inhibited tumor growth and metastasis spread while also normalizing the architecture of the blood arteries. As a result, OTX008 seems to be a cutting-edge method of combating cancer, and the purpose of this clinical phase I trial is to assess OTX008 therapy in patients with advanced solid tumors. It was

Table II: Details of clinical trials w.r.t galectin inhibitors in various cancers (Taken from https://clinicaltrials.gov/)

NCT Number	Target	Inhibitor/ Drug	Phase	Type of cancer	Type of the study
NCT02575404	Galectin-3	GR-MD-02	Phase-1	Non-Small Cell, Lung cancer and Head and Neck Squamous Cell Carcinoma	GR-MD-02 Pembrolizumab in Melanoma, Non-small cell Lung cancer and Squamous cell Head and Neck patients.
NCT05240131	Galectin-3	GB1211	Phase-1	Non-small cell lung cancer	A Study to Investigate the Safety and Efficacy of GB1211 (a Galectin-3 Inhibitor) in Combination with Atezolizumab in Patients with Non-Small Cell Lung cancer.
NCT01724320	Galectin-1	OTX008	Phase-1	Advanced solid tumors	A Phase I, First-in-man Study of OTX008 Given Subcutaneously as a Single Agent to Patients with Advanced Solid tumors.
NCT01723813	Galectin-3	GM-CT-01	Phase-1& 2	Metastatic Melanoma	Peptide vaccinations plus GM-CT-01in Melanoma
NCT01681823	Galectin-3	PectaSol-C Modified Citrus Pectin (MCP)	Phase-3	Prostatic Neoplasms	Effect of Modified Citrus Pectin on PSA Kinetics in Biochemical Relapsed PC with Serial Increases in PSA

intended to administer OTX008 for up to three weeks before reporting dose-limiting toxicity. To determine the recommended dose for each patient receiving OTX008, the DLT had to be evaluated throughout the first 21 days (3 weeks) of treatment (Recommended Dose). Although there are currently only 20 study participants, recruitment continues to proceed ahead. Even though a Phase I trial in patients with advanced solid tumors is currently described as actively recruiting (the most recent update was given in 2012), the program's overall status remains a mystery since Merck acquired OncoEthix in 2014(54).

The clinical study w.r.t GM-CT-01/DAVANAT included 20 participants, all of whom had received at least two previous chemotherapy treatments. While a series of Phase II trials in cancer patients in the United States and Europe were planned, they were never started, with the status described as "withdrawn/terminated" on www.clinicaltrials.gov.

Pectasol-C clinical trials aim was to evaluate the Prostate Specific Antigen (PSA) Kinetics in Men with Biochemical Relapsed Prostate Cancer and Serial Increases in PSA Levels were the main outcome measure. [Time period: endpoint at 6 months]. To demonstrate the efficiency of the modified citrus pectin which is MCP, PSA doubling time increase was used. Dietary Supplement PectaSol-C Modified Citrus Pectin (MCP) was the intervention. Administering PectaSol-C MCP orally (4.8 grams in six capsules three times a day away from food).There has also been recording of any negative impacts or positive effects that fall within the scope of the study (55).

In addition to cancer, the inhibitors identified were investigated in the treatment of nonalcoholic steatohepatitis, cirrhosis, liver fibrosis, and pulmonary fibrosis. Galectin Therapeutic based GR-MD-02 is a gal-3 inhibitor that is now being tested in a phase 3 clinical trial as a therapy for Nonalcoholic Steatohepatitis Cirrhosis (NCT04365868)(56). Galecto Inc. produced TD139 (GB0139), a gal-3 inhibitor that is being tested in a phase 2b clinical trial for the treatment of Idiopathic Pulmonary Fibrosis (NCT03832946)(57). Furthermore, it is being evaluated as a quick experimental therapy to treat COVID-19 in Phase 3 trials (NCT04473053)(58). GB1211, an gal-3 inhibitor developed by Galecto Inc., has been proven to be well tolerated in pre-clinical and Phase 1 investigations and is currently slated to enter a Phase 2a trial to treat liver fibrosis (NCT03809052) in addition to lung cancer(59). However, the challenges have to be addressed in addition to knowing their potential inhibitory activity. Many mono and di saccharide-based ligands have been investigated for their ability to inhibit galectins. Thiodigalactoside was one of the first small organic molecules to enter clinical trials as a galectin inhibitor, such as GB0139/TD139. The fascination in these inhibitors motivated synthetic chemists to work on techniques to simplify the production of these complex saccharide-based compounds. However, research demonstrated that GB0139/TD139 had limited intracellular activity and was swiftly removed from the circulation.

Furthermore, the synthetic technique for developing disaccharides like TD139 proved highly rigorous. Because of the difficult synthesis and poor pharmacokinetic properties of thiodigalactoside analogues, as well as the longer biological half-life of monosaccharide inhibitors, major pharmaceutical companies are increasingly interested in developing inhibitors with improved pharmacokinetic properties (60).

Galectin-targeted cancer therapies have showed promise in preclinical investigations, but before they can be applied in clinical settings, a number of issues and constraints need to be resolved. The lack of selectivity in some galectin inhibitors is a significant problem. Different galectins may have different roles in the development of cancer. Galectins are a class of proteins with a variety of functions (61). Therefore, it's critical to create inhibitors that specifically target the galectin(s) associated with a

given cancer type or stage. Understanding the expression patterns and roles of various galectins in cancer cells and their microenvironment is essential for this. The possible toxicity of galectin inhibitors is an additional difficulty. Inhibiting galectins may have unanticipated effects since they are essential for many physiological processes that occur naturally, including immunological control and tissue repair. For instance, Galectin 3 has been demonstrated to support T cell activation and survival, and its suppression may reduce the body's ability to resist tumors(62). Therefore, it is crucial to carefully assess the galectin inhibitors tolerability profiles in preclinical experiments and clinical research. Some galectin antagonists may also have inadequate absorption into tumor tissues or poor pharmacokinetic qualities, which might result in limited effectiveness. Small-molecule inhibitors, for instance, might be quickly digested or eliminated from the body before they arrive to their target site(63). Galectin inhibitors' pharmacokinetic qualities must therefore be optimized by changing their chemical makeup or delivery systems. Regulatory approval and medication development problems are another factor. Galectin-targeted medicines are still in the early stages of development, and there is little practical knowledge of how to test and approve them in clinical settings(64). Before approving these medicines for use in clinical settings, regulatory bodies might also seek more information on safety and efficacy.

The following is the brief summary of the advantages and limitations of different inhibitor types and classes.

A. A family of compounds known as small molecule inhibitors have been designed to specifically target galectins by attaching to their carbohydrate recognition domains (CRDs). These inhibitors can be created with good pharmacokinetic features, oral administration, and high specificity and affinity for a particular galectin. TD139 and GR-MD-02 are two examples of small molecule inhibitors that have demonstrated promise in both preclinical research and clinical trials(65).

Advantages: Small molecule inhibitors are advantageous since they are relatively simple to create and alter. They may be given orally and have strong pharmacokinetic qualities. They can be made to have high affinity and specificity for a particular galectin.

Limitations: They may not penetrate cell membranes effectively and may need high doses to produce therapeutic effects. Small molecule inhibitors may lack selectivity for a specific galectin and may block other galectins that are crucial for normal physiological activities(66).

B. Monoclonal antibodies (mAbs) can be engineered to target particular epitopes on the surface of galectins. These mAbs can be given subcutaneously or intravenously and can be designed to have great specificity and affinity for a particular galectin. GCS-100, which targets GAL3, and MGD007, which targets GAL1, are two notable examples of mAbs in galectin research.

Advantages: High affinity and specificity monoclonal antibodies can be created for a certain galectin. They can be given subcutaneously or intravenously.

Limitations: Solid tumors may be too large for monoclonal antibodies to penetrate effectively. They might trigger immunological reactions or infusion-related side effects(67).

C. Delivering genetic material to cells in order to control gene expression is the process used in gene therapies. Gene therapies can be utilized to silence or overexpress particular galectins in cancer cells in the context of galectin-targeted cancer therapy. Small interfering RNA (siRNA) and CRISPR/Cas9-mediated gene editing are two notable examples of gene therapies.

Advantages: Gene therapies can be used to selectively target specific galectins in cancer cells. They can be designed to have long-lasting effects.

Limitations: To fully realize the potential of gene therapy, which is long-term therapeutic benefit or, ideally, a cure, it is crucial to have a thorough understanding of the barriers to therapeutic intervention and to develop strategies to get over them. Success will also depend on finding an appropriate therapeutic gene(s) that may hinder the spread of the condition (68).

DISCUSSION

Lectins are not the most accessible targets for the development of inhibitors since they often have deeply positioned and hydrophilic binding grooves. Additionally, the extremely conserved residues in the galectin family make it challenging to produce particular inhibitors. Numerous research teams have attempted to solve this issue and are still working on it, generally by modifying or swapping out the galactose or thio-galactoside component. The search for potent monovalent and divalent inhibitors has advanced significantly, but less is known about other groups of gal-1 and gal-3 inhibitors, such as peptides, peptidomimetics, and heterocyclic compounds. In order to gain a greater understanding how these compounds bind to the carbohydrate recognition domain, it may be possible to design and use non-carbohydrates in place of traditional sugar-based ligands. Additionally, if more advanced techniques are applied, the current rapid surge of small molecule inhibitors targeting galectins and lectins in particular has the potential to give us new sources of structural information that weren't previously obvious. For instance, studies of protein crystallography using inhibitors of the heterocyclic gal1 and gal-3 may

reveal specific allosteric regions. The quest still lacks a few pieces, though. There is currently no proof that any of the galectin inhibitors based on heterocyclic molecules bind to the CRD of the galectins. Various in-silico technologies have backed the findings mentioned, which supports the authors' statements that these compounds communicate with residues of the active site in galectin CRD to bind to it. A crystallographic study of galectins using a handful of the known small molecule inhibitors would provide strong evidence in this regard. Incorporating machine learning algorithms based on current inhibitors could help investigators better grasp the essential structural characteristics needed to create innovative, tailored non-carbohydrate galectin inhibitors.

CONCLUSION

As previously noted, galectins play an important role in cancer progression by modifying the tumour microenvironment, angiogenesis, metastatic potential, and immune response. The existing data suggest that galectin inhibitors could play a role in cancer treatment. It has emerged as a potential therapeutic target for a variety of serious diseases due to its widespread expression throughout the body and role in cell-cell communication influencing adhesion, migration, growth and other processes.

Recent biotechnology and pharmaceutical interest has resulted in clinical trials of various new compounds against galectins. So far, they have become pharmacological targets, opening up the possibility of translational research for other carbohydrate binding proteins. The approaches will be developed and recognised as an untapped source of innovative treatments for unmet medical needs. Based on these findings, we believe galectins are key players in cancer progression and metastasis. Although the altered expression of galectins in various cancer types is totally unknown, further study can aid in assessing their innovative clinical uses, since some of them can be used to predict prognoses, diagnoses, and new therapeutics. Furthermore, the deep knowledge of galectins, as well as the processes by which it can be controlled, should be investigated systematically. The large number of publications devoted to glycobiology and its applications should persuade everyone that glycoconjugates have entered their golden age. The study's interrelated notions of galectins and their effective binding will help us comprehend the significance in the field of tumour biology and will provide the groundwork for future anti-cancer strategies. The quest of the early twenty-first century will be to understand the interactions between genes, proteins, glycol-conjugates, and cell activity.

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