Galectins as therapeutic targets for hematological malignancies: a hopeful sweetness

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Abstract: Galectins are family of galactose-binding proteins known to play critical roles in inflammation and neoplastic progression. Galectins facilitate the growth and survival of neoplastic cells by regulating their cross-talk with the extracellular microenvironment and hampering anti-neoplastic immunity. Here, we review the role of galectins in the biology of hematological malignancies and their promise as potential therapeutic agents in these diseases.

Keywords: Galectins; galectin-3 (Gal-3); lymphomas; leukemia; multiple myeloma (MM)

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Introduction

Galectins are a sub-family of lectins, proteins that bind to carbohydrates complexed with proteins and lipids (glycoconjugates), normally found on the cell surface and in the extracellular matrix (1). The main functions of lectins are to mediate cell-cell and cell-matrix adhesion, modulation of extracellular signal transductions and recognitions of pathogens. Galectins are distinct from other lectins because of their ability to bind to β-galactoside glycoconjugates, which accounts for a consensus aminoacid sequence shared by different members of the galectin family (2). At present, sixteen members of the galectin family have been identified. Based on the number of consensus sequences forming the carbohydrate-recognition domains (CRD, 130 amino acid-long), galectins are classified into two main groups; galectins with one or two-CRD (3). Different galectins display specificity for different oligosaccharides, depending on which saccharide is attached to the galactose (4), and they have a wide variety of functions including regulating adhesion, migration, polarity, chemotaxis, proliferation, apoptosis, and differentiation in all tissues (5).

In the hematopoietic system, galectins play a major physiologic role due to their pleiotropic effects in the bone marrow and in the lymphatic microenvironment during the process of lymphopoiesis. The interactions between hematopoietic and non-hematopoietic (stromal) cells in the bone marrow and other immune organs, such as the thymus, are essential to create the required hematopoietic niches where blood cells precursors can reside, transit, and mature. Galectins-1 (Gal-1), -3, -8, and -9 are abundantly expressed by thymic epithelial cells (TECs), and they mediate the pro-apoptotic effect exerted by TECs on pre-thymocytes during the process of T cell deletion (6-8). In contrast, regulatory T-cell differentiation is facilitated by Gal-1 and -10, contributing to the immunosuppressive activity of these cells (9,10). Gal-1 is also secreted by

stromal cells of the bone marrow and acts as a pre-BCR unconventional ligand, stimulating the proliferation and survival of B-cell precursors (11). Outside the bone marrow, B lymphocytes are also sensitive to galectins expressed in lymphoid organs, such as the spleen, lymph nodes and other peripheral tissues. For instance, Gal-1 is required for the differentiation of germinal center (GC) B cells into immunoglobulin-secreting plasma cells (12,13), while Gal-3 drives B cell differentiation towards a memory phenotype (14).

In the following paragraphs, we focus on their effects on malignant T and B cells, and we discuss the potential of galectin-modulating therapies for the treatment of hematological neoplasms.

Galectin in lymphomas

Lymphomas are neoplasms derived from proliferating B-lymphocytes, T-lymphocytes, and natural killer (NK) cells. Lymphomas are further divided into two classes based on cancer cell morphologies: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) (15). Excluding mantle cell and lymphoblastic lymphoma, B-cell NHL originates from GC cells or post-GC B-cells, the most common being diffuse large B-cell lymphoma (DLBCL) (16,17).

Galectins are known for their involvement in key cellular processes as a result of β-galactoside-containing glycoconjugates recognition through their CRD (16,18). Galectins participate in a variety of pathophysiological events including cell proliferation, apoptosis, inflammatory responses, and tumor progression, and their role in the biology of lymphomas has recently attracted significant interest. Of the 16 existing members of the galectin family, Gal-1, -3, and -7 have been the focus of attention due to their role participation in the progression and prognosis of NHL, especially DLBCL and anaplastic large cell lymphoma (ALCL), as well as classic HL (18-20).

Gal-1 is an extracellular matrix protein expressed on the cell surfaces of HL and ALCL and is up-regulated on Burkitt lymphoma (BL) cells (21-23). Increased Gal-1 serum levels are an indicator of increased tumor burden in HL patients (22) and has been shown to play regulatory roles involving inflammatory responses, angiogenesis, and tumor progression (19). Gal-1 modulates cell adhesion and invasion of extracellular matrix in ALCL (23), and also binds to CD45, a tyrosine phosphatase receptor responsible for signaling and survival in B- and T-cells. Gal-1 binding causes CD45 clustering, which inhibits CD45 function (22). HL Reed-Sternberg (RS) cells secrete Gal-1, which causes a rest period during a cell cycle and induces T- and B-cell lymphoma cell apoptosis through CD45 clustering (21,22). CD45 interaction with Gal-1 regulate of T-cell survival and signaling by modulating T-cell CD45 phosphatase activity (16,23). Investigators have studied the ability of Gal-1 to selectively kill Th1, Th17, and cytotoxic T cells. Targeting of Th1, Th17, and cytotoxic T-cells results in an immunosuppressive environment in which RS cells are able to evade immune detection and apoptosis (19,22,24). While Th1 and Th17 T-cells are killed off, varying cell surface glycoprotein sialylation allow for Th2 T-cells to evade apoptosis thus explaining the immunosuppressive microenvironment characterized by the presence of Th2/Treg cells (19,24).

Gal-3 is expressed in normal memory B cells and lymphomas including DLBCL, primary effusion lymphoma (PEL), and multiple myeloma (MM), but lowly expressed in normal B-lymphocytes of the GC and plasma cells (25). Gal-3 has not been identified in marginal zone or follicular lymphomas (FL) but is present in aggressive lymphomas, suggesting its involvement in processes associated with large tumor loads (26). Gal-3 has no transmembrane domain and is expressed in the nucleus, both intracellular and extracellular plasma membrane surfaces, as well as mitochondria, where it interacts with Bcl-2 to prevent apoptosis (16). In one study, high cytoplasmic and nuclear Gal-3 expression was observed in DLBCL patients and cell lines, MM patients and plasma cell-derived lines, and PEL cell lines originating from plasma or plasma cell-like B-cell maturation. Significant Gal-3 expression was also observed in DLBCL and MM patient macrophage and dendritic cells indicating macrophage and dendritic cells might contribute to extracellular Gal-3 levels. Gal-3 expression has not been detected in GC-derived BL patients and cell lines, GC-derived FL patients, and post-GC-derived B-cell lymphoma patients (nodal and extranodal marginal zone, MALT/BALT, and B-small lymphocytic lymphomas). Overall, Gal-3 was absent in BL and FL, but expressed in DLBCL, PEL, and MM. These results defined Gal-3 expression as independent of the c-MYC aberrant expression responsible for the rapid proliferative rate seen in BL. Human tonsil B-cell populations were also tested for Gal-3 expression, with the lowest level of Gal-3 expression found in GC dendritic reticular cells and CD138+ plasma cells. The investigators also noted high Gal-3 expression in naïve (CD17–/IgD+) and memory B cells (CD10–/CD27+/IgD–), but Gal-3 was not found to be related to or affected

by EBV infection, indicating that Gal-3 up-regulation is not caused by viral transformation (25). Gal-3 also binds to ligand 90K, a large tumor-associated antigen that mediates cell-to-cell adhesion. High 90K and Gal-3 expression is correlated with lower complete response, increased rates of progression, and lower overall survival rates in lymphomas. Gal-3 expression may identify aggressive tumor histologies, since the Gal-3/90K complexes promote homotypic cell aggregates, through the cross-linking of Gal-3, that display increased survival in the bloodstream during the metastatic process (26). Investigators have also shown that Gal-3 expression plays a protective role against cell death mediated by anti-Fas antibody (25,26).

In lymphoma cells, Gal-7 enhances cell dissemination via matrix metalloproteinase-9 (MMP-9) expression, a metastatic gene associated with poor prognosis in NHL (27). Not only lymphoma cells expressing Gal-7 have high MMP-9 expression, but recombinant Gal-7 induces MMP-9 expression in lymphoma and inhibition of Gal-7 binding leads to a loss of MMP-9 expression, all of which indicate Gal-7 controls tumor behavior through expression of the metastatic gene MMP-9 (28). Thus, Gal-7 offers some promise as a therapeutic target for lymphomas due to its significant high expression in mature B-cell neoplasms *vs.* low expression in normal B-cells (27).

Galectins in leukemia

Different members of the galectin family have been shown to play a role in various types of leukemias. For example, chronic lymphocytic leukemia (CLL) patients have higher levels of Gal-1 in their plasma, and such expression is associated with disease progression (29). Gal-1 is also secreted by myeloid cells and influences leukemic B-cell biology. As an example, Gal-1 stimulates IL-10 and CCL3 production by malignant cells in a murine experimental model, two key molecules for the survival of the CLL clone (29).

Gal-3 is highly expressed by chronic myelogenous leukemia (CML) cells in the bone marrow (30). Interestingly, co-culturing bone marrow stromal cells (BMSC) with CML cell lines induced the expression of Gal-3, causing drug resistance *in vitro*. Similarly, Gal-3 overexpression in CML cells increased their proliferative and chemotactic capacity, as well as their resistance to therapeutic drugs (30). Finally, Gal-3 facilitates CML cell migration and long-term residence in the bone marrow (30).

Cheng *et al.* have studied Gal-3 mRNA expression in 280 samples from AML patients and found that Gal-3 expression was an independent poor prognostic factor, regardless of age, leukocyte counts or karyotype, and was proven to be reliable biomarker in AML (31). AML is frequently associated with a defective T-cell response that facilitates disease progression (32). A potential explanation for this observation is that Gal-9 and its ligand, T cell immunoglobulin mucin-3 (TIM-3), were shown to contribute to T-cell exhaustion in a murine model of AML (33). AML-bearing mice displayed high TIM-3 on in their CD8+ T lymphocytes, and this was inversely correlated with the expression of IFN-γ, a marker of activated T-cells. Of note, TIM-3 is also highly expressed on most human AML cells, and it is required for their engraftment in the bone marrow of experimental mice (33).

Galectins in MM

MM is a malignancy of plasma cells associated with bone marrow and organ infiltration, decreased hematopoiesis, osteolytic lesions, hyercalcemia, infections and renal dysfunction (34). Galectins have been shown to play a role in cell-cell and cell-matrix adhesion, leading to tumor formation (29). Gal-3 is expressed by MM cells and is found in the cytoplasm where it actively suppresses apoptosis. Gal-3 can also be secreted into the extracellular space where it interacts with cell surface molecules or translocate into the nucleus where it can be involved in a variety of biological processes including up-regulation of the NF-$_K$B/AKT system and MCL-1/BCL-X_L resulting in down-regulation of NOXA and $p21^{Cip1}$ and consequent increased cell survival (35).

Gal-3 has also been shown to be an important mediator of MM cell survival. In a study done by Streetly *et al.* the Gal-3 inhibitor GCS-100 induced cell death signals related to down regulation of MCL-1/BCL-X_L, MCL-1 in MM cells (35). This down regulation led to the up regulation of NOXA and $p21^{Cip1}$, which caused the down regulation of Cyclin E and Cyclin D2. They also noticed the reduction of activated NF-$_K$B/AKT, all of which contributed to apoptosis via both the extrinsic (caspase-8) and the intrinsic (caspase-9) pathways (35). Another study by Mirandola *et al.* used Gal-3C, a truncated dominate negative form, in conjunction with the proteasome inhibitor bortezomib (Bor) in MM cells (36). They found that Gal-3C diminished the growth of MM cells *in vivo* and displayed an additive anti-myeloma effect when used with Bor. Gal-3C also caused inhibition of MM cell-induced angiogenesis as evidenced by decreased HUVEC migration. These investigators also observed Gal-3C

inhibition of chemotaxis stimulated by the chemokine SDF-1α. This chemokine, along with its receptor CXCR4, are regulators of migration and homing of MM cells to the bone marrow (36).

Gal-9 is characterized by having two different CRD carbohydrate recognition domains that recognize different sugar binding target molecules, allowing for cross-linking. Gal-9 has been shown to inhibit the growth of five different myeloma cell lines through activation of capsase-8, -9, and -3 pathways. These investigators also found that Gal-9 activated the JNK and p38 MAP kinase pathways, reducing cell proliferation *in vivo* and inducing cell death. Using a nude mice xenograft model, they found that Gal-9 also displayed strong inhibition of human myeloma cells (37).

Clinical implications

As previously discussed, galectins are known to be involved in multiple biological processes in hematologic malignancies, including apoptosis, regulation of cellular homeostasis, angiogenesis, cell proliferation, drug resistance and neoplastic progression (38,39). Therefore, galectins represents a potentially promising therapeutic target for the treatment of these neoplastic conditions.

Lymphoma

Lotan *et al.* have demonstrated that anti-Gal-1 antibodies can prevent the adhesion of murine large-cell lymphoma cells to hepatic sinusoidal endothelial cells or lung microvessel endothelial cells (40). Upon Gal-1 exposure, T lymphocytes undergo apoptosis through the deactivation of CD45 protein tyrosine phosphatase (PTP). Alteration in glycosylation of CD45 also has been shown to inhibit growth of BL Burkitt's cell lines (21). Suzuki *et al.* have used Gal-1 to inhibit CD45 PTP activity in a human ALCL cell line, suggesting that inhibition of CD45 PTP by Gal-1 could be a potential mechanism to induce cell death in human lymphoma (41). DLBCL cell lines treated with swainsonine (SW), an inhibitor of the synthesis of complex type N-linked oligosaccharides, and benxyl-GalNAx (BZGalNAc), an inhibitor of O-glycosylation, resulted in interference of Gal-1-induced apoptosis, *in vitro*. These findings suggest that decreasing CD45 N- or O-glycans, by SW and BZGalNAx treatment respectively, can alter the interaction between CD45 with Gal-1 in DLBCL cells (42). The importance of cell surface protein glycosylation is supported by the observation that DLBCL has a more aggressive behavior and worse prognosis if they lack non-sialylated L-PHA-reactive oligosaccharides (43-46). It has been hypothesized that loss of L-PHA-reactive oligosaccharides prevents Gal-1-mediated apoptosis, leading to aggressive behavior and cell survival in DLBCL with high cell surface sialylation (41).

Gal-3 has antiapoptotic activity (38) and also could be useful as a potential marker to differentiate between DLBLC and BL (25,47). As previously discussed, high expression of Gal-3 has been found in DLBCL and PEL, suggesting it could serve as a therapeutic target. Indeed, Gal-3 expression is protective from Fas-induced apoptosis, a key pathway of B-cell elimination *in vivo* (25). A truncated form of Gal-3, known as Gal-3C, has been used to inhibit Gal-3 anti-apoptotic effects. Gal-3C differs from Gal-3 in that it lacks the N-terminal domain used to protect against apoptosis through homotypic multimerization and molecular crooslinking (48). Gal-3C has been shown to block Gal-3 supported B-cell survival and in one study Gal-3C transfected PEL cells saw a 90-95% increase in apoptosis after anti-Fas treatment (25). Thus, blocking Gal-3 with may abrogate its anti-apoptotic properties in mature B-cell-derived lymphomas resulting in a synergistic effect with conventional anti-lymphoma treatments.

Demers *et al.* have also demonstrated that lymphoma cells transfected with a plasmid encoding antisense Gal-7 cDNA showed decreased potential to disseminate and invade peripheral organs in an experimental model (27). These investigators also confirmed elevated expression of Gal-7 in human lymphoid malignancies but not in normal B cell. These findings suggest that targeting of Gal-7 could be potential therapeutic strategies in the treatment of lymphoid malignancies.

Leukemia

As previously discussed, galectins have been found to be elevated in several leukemic processes. Gal-3 is found to be overexpressed in bone marrow samples of acute lymphocytic leukemia (ALL) patients when compared to healthy controls (49-51). Interestingly Gal-3 was not located on ALL cell surfaces, but was detected on stromal cells. Overexpression of Gal-3 enhanced resistance of TSXL2 cells to nilotinib and vincristine. As expected, Gal-3 negative cells were more sensitive to nilotinib and vincristine as opposed to Gal-3 positive pre B-ALL carrying the Bcr/Abl transformation. Therefore, the presence of Gal-3 protein expression in ALL can be a potential marker of drug resistance in this disease.

Gal-3 expression in CML cells is induced by co-culture with BMSC, and this paracrine growth loop is mediated by interfering with the action of the growth inhibitory SERPINA1-albumin complex (52). These preliminary data suggest Gal-3 inhibitory strategies may represent a potential treatment strategy against certain leukemias.

Plasma Gal-1 levels have also been found to be significantly elevated in patients with CLL, compared to healthy samples (29). Gal-1 levels were statistically higher in patients with high risk CLL (those with CD38 and ZAP 70 expression) indicating Gal-1 expression may be associated with poor outcome in this disease. Thus, therapeutic interventions that inhibit Gal-1 may emerge as a potential treatment option for patients with high-risk CLL.

Persistence of leukemic stem cells (LSCs) following standard systemic therapy is thought to mediate treatment refractoriness and relapse in AML. Since the Gal-9 receptor TIM-3 is expressed on AML LSCs, but not on normal hematopoietic stem cell, myelo-erythroid or lymphoid progenitor cells, Gal-9 targeting could be exploited as a promising therapeutic strategy in this disease without affecting normal hematopoiesis (53). Moreover, Gal-9-TIM3 binding on T-helper 1 cells has been shown to promote cell death resulting in inhibition of T cell-mediated immunity (54,55). Thus, inhibition of Gal-9 may not only target LSCs but also restore T-cell immunity in AML.

Multiple myeloma (MM)

Galectin targeted therapies may also offer new hope in the treatment of MM. For example, the use of protease-resistant Gal-9 has been shown to inhibit MM cell growth *in vitro* and may represent a new therapeutic modality in this disease (37). The N-terminally truncated form of Gal-3, Gal-3C, has also been shown to inhibit MM cell proliferation *in vitro*, exert significant anti-tumor activity as monotherapy and result in additive anti-myeloma effects when used in conjunction with Bor, in an *in vivo* model of MM (34,36). Moreover, the Gal-3 inhibitor GCS-100, has also demonstrated a significant reduction in MM cell proliferation, viability, and resistance by inducing apoptosis via both caspase and non-caspase dependent cell death (35). Gal-1 has been shown to be a strong survival factor for MM cells and also represents a potential therapeutic target in this disease (56-58). Finally, Gal-1 has been associated with immunoglobulin production during plasma cell development, opening a window of opportunity for the development of immunomodulatory strategies in patients with plasma cell dyscrasias (13).

In conclusion, an emerging body of experimental work has demonstrated that several members of the galectin family of proteins are important in the pathophysiology of many hematologic malignancies. These observations suggest a potential opportunity to exploit these molecules as therapeutic targets in these diseases. However, due to the complexity of galectins' molecular and cellular interactions, it is imperative to further elucidate and understand the distinct roles that different galectins may play in the biology of hematologic neoplasms before they could be develop as therapeutic options for patients afflicted with these diseases.

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